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(21) International Application Number: PCT/US97/18703 (22) International Filing Date: 23 October 1997 (23.10.97) (30) Priority Data: 60/034,044 25 October 1996 (25.10.96) US (71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MCWHERTER, Charles, A. [US/US]; 16564 Thunderhead Canyon Court, Ellisville, MO 63011 (US). FENG, Yiqing [US/US]; 423 Mission Court, St. Louis, MO 63130 (US). SUMMERS, Neena [US/US]; 1203 Saddlemaker, St. Charles, MO 63304 (US). (74) Agents: BENNETT, Dennis, A. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: CIRCULARLY PERMUTED ERYTHROPOIETIN RECEPTOR AGONISTS**(57) Abstract**

Disclosed are novel Erythropoietin receptor agonist proteins, DNAs which encode the Erythropoietin receptor agonist proteins, methods of making the Erythropoietin receptor agonist proteins and methods of using the Erythropoietin receptor agonist proteins.

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CIRCULARLY PERMUTED ERYTHROPOIETIN RECEPTOR AGONISTS

The present application claims priority under Title 35,
United States Code, §119 of United States Provisional
5 application Serial No. 60/034,044, filed October 25,
1996.

FIELD OF THE INVENTION

The present invention relates to human
10 Erythropoietin (EPO) receptor agonists. These EPO
receptor agonists retain one or more activities of
native EPO and may also show improved hematopoietic
cell-stimulating activity and/or an improved activity
profile which may include reduction of undesirable
15 biological activities associated with native EPO and/or
have improved physical properties which may include
increased solubility, stability and refold efficiency.

BACKGROUND OF THE INVENTION

20 Colony stimulating factors which stimulate the
differentiation and/or proliferation of bone marrow
cells have generated much interest because of their
therapeutic potential for restoring depressed levels of
hematopoietic stem cell-derived cells.

25

Erythropoietin is a naturally-occurring
glycoprotein hormone with a molecular weight that was
first reported to be approximately 39,000 daltons (T.
Miyaki et al., *J. Biol. Chem.* 252:5558-5564 (1977)).
30 The mature hormone is 166 amino acids long and the
"prepro" form of the hormone, with its leader peptide,
is 193 amino acids long (F. Lin, U.S. Patent No.
4,703,008). The mature hormone has a molecular weight,
calculated from its amino acid sequence, of 18,399
35 daltons (K. Jacobs et al., *Nature* 313:806-810 (1985);
J. K. Browne et al., *Cold Spring Harbor Symp. Quant.*
Biol. 5:1693-702 (1986)).

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The first mutant erythropoietins (i.e., erythropoietin analogs), prepared by making amino acid substitutions and deletions, have demonstrated reduced or unimproved activity. As described in U.S. Patent NO. 4,703,008, replacement of the tyrosine residues at positions 15, 40 and 145 with phenylalanine residues, replacement of the cysteine residue at position 7 with an histidine, substitution of the proline at position 2 with an asparagine, deletion of residues 2-6, deletion of residues 163-166, and deletion of residues 27-55 does not result in an apparent increase in biological activity. The Cys'-to-His' mutation eliminates biological activity. A series of mutant erythropoietins with a single amino acid substitution at asparagine residues 24, 38 or 83 show severely reduced activity (substitution at position 24) or exhibit rapid intracellular degradation and apparent lack of secretion (substitution at residue 38 or 183). Elimination of the O-linked glycosylation site at serine126 results in rapid degradation or lack of secretion of the erythropoietin analog (S. Dube et al., *J. Biol. Chem.* 33:17516-17521 (1988)). These authors conclude that glycosylation sites at residues 38, 83 and 126 are required for proper secretion and that glycosylation sites located at residues 24 and 38 may be involved in the biological activity of mature erythropoietin.

Deglycosylated erythropoietin is fully active in in vitro bioassays (M. S. Dorsdal et al., *Endocrinology* 116:2293-2299 (1985); U.S. Patent No. 4,703,008; E. Tsuda et al., *Eur J. Biochem.* 266:20434-20439 (1991)). However, glycosylation of erythropoietin is widely accepted to play a critical role in the in vivo activity of the hormone (P. H.. Lowy et al., *Nature* 185:102-105 (1960); E. Goldwasser and C. K. H.. Kung, *Ann. N.Y. Acad. Science* 149:49-53 (1968); W. A. Lukowsky and R.

- H.. Painter, *Can. J. Biochem.* :909-917 (1972); D.W. Briggs et al., *Amer. J. Phys.* 201:1385-1388 (1974); J.C. Schooley, *Exp. Hematol.* 13:994-998; N. Imai et al., *Eur. J. Biochem.* 194:457-462 (1990); M.S. Dordal et al.,
5 *Endocrinology* 116:2293-2299 (1985); E. Tsuda et al., *Eur. J. Biochem.* 188:405-411 (1990); U.S. Patent No. 4,703,008; J.K. Brown et al., *Cold Spring Harbor Symposia on Quant. Biol.* 51:693-702 (1986); and K. Yamaguchi et al., *J. Biol. Chem.* 266:20434-20439 (1991).
10 The lack if in vivo biological activity of deglycosylated analogs of erythropoietin is attributed to a rapid clearance of the deglycosylated hormone from the circulation of treated animals. This view is supported by direct comparison of the plasma half-life
15 of glycosylated and deglycosylated erythropoietin (J.C. Spivak and B.B. Hoyans, *Blood* 73:90-99 (1989), and M.N. Fukuda, et al., *Blood* 73:84-89 (1989).

Oligonucleotide-directed mutagenesis of
20 erythropoietin glycosylation sites has effectively probed the function of glycosylation but has failed, as yet, to provide insight into an effective strategy for significantly improving the characteristics of the hormone for therapeutic applications.

25 A series of single amino acid substitution or deletion mutants have been constructed, involving amino acid residues 15, 24, 49, 76, 78, 83, 143, 145, 160, 162, 163, 164, 165 and 166. In these mutants are altered
30 the carboxy terminus, the glycosylation sites, and the tyrosine residues of erythropoietin. The mutants have been administered to animals while monitoring hemoglobin, hematocrit and reticulocyte levels (EP No. 0 409 113). While many of these mutants retain in vivo
35 biological activity, none show a significant increase in their ability to raise hemoglobin, hematocrit or

reticulocyte (the immediate precursor of an erythrocyte) levels when compared to native erythropoietin.

Another set of mutants has been constructed to probe the function of residues 99-119 (domain 1) and residues 111-129 (domain 2) (Y. Chern et al., *Eur. J. Biochem.* 202:225-230 (1991)). The domain 1 mutants are rapidly degraded and inactive in an *in vitro* bioassay while the domain 2 mutants, at best, retain *in vitro* activity. These mutants also show no enhanced *in vivo* biological activity as compared to wild-type, human erythropoietin. These authors conclude that residues 99-119 play a critical role in the structure of erythropoietin.

15

The human erythropoietin molecule contains two disulfide bridges, one linking the cysteine residues at positions 7 and 161, and a second connecting cysteines at positions 29 and 33 (P.H. Lai et al., *J. Biol. Chem.* 261:3116-3121 (1986)). Oligonucleotide-directed mutagenesis has been used to probe the function of the disulfide bridge linking cysteines 29 and 33 in human erythropoietin. The cysteine at position 33 has been converted to a proline residue, which, mimics the structure of murine erythropoietin at this residue. The resulting mutant has greatly reduced *in vitro* activity. The loss of activity is so severe that the authors conclude that the disulfide bridge between residues 29 and 33 is essential for erythropoietin function (F.K. Lin, *Molecular and Cellular Aspects of Erythropoietin and Erythropoiesis*, pp. 23-36, ed. I.N. Rich, Springer-Verlag, Berlin (1987)).

U.S. Patent No. 4,703,008 by Lin, F-K. (hereinafter referred to as "the '008 patent") speculates about a wide variety of modifications of EPO, including addition, deletion, and substitution analogs of EPO.

5

The '008 patent does not indicate that any of the suggested modifications would increase biological activity *per se*, although it is stated that deletion of glycosylation sites might increase the activity of EPO produced in yeast (See the '008 patent at column 37, lines 25-28). Also, the '008 patent speculates that EPO analogs which have one or more tyrosine residues replaced with phenylalanine may exhibit an increased or decreased receptor binding affinity.

10

Australian Patent Application No. AU-A-59145/90 by Fibi, M et al. also discusses a number of modified EPO proteins (EPO muteins). It is generally speculated that the alteration of amino acids 10-55, 70-85, and 130-166 of EPO. In particular, additions of positively charged basic amino acids in the carboxyl terminal region are purported to increase the biological activity of EPO.

U.S. Patent No. 4,835,260 by Shoemaker, C.B. discusses modified EPO proteins with amino acid substitutions of the methionine at position 54 and asparagine at position 38. Such EPO muteins are thought to have improved stability but are not proposed to exhibit any increase in biological activity relative to wild type EPO.

WO 91/05867 discloses analogs of human erythropoietin having a greater number of sites for carbohydrate attachment than human erythropoietin, such as EPO (Asn⁶⁹), EPO (Asn¹²⁵, Ser¹²⁷), EPO (Thr¹²⁵), and EPO (Pro¹²⁴, Thr¹²⁵).

WO 94 /24160 discloses erythropoietin muteins which have enhanced activity, specifically amino acid substitutions at positions 20, 49, 73, 140, 143, 146, 147 and 154.

WO 94/25055 discloses erythropoietin analogs, including EPO (X¹¹, Cys¹³⁹, des-Arg¹⁶⁶) and EPO (Cys¹³⁹, des-Arg¹⁶⁶).

5

Rearrangement of Protein Sequences

In evolution, rearrangements of DNA sequences serve an important role in generating a diversity of protein structure and function. Gene duplication and exon shuffling provide an important mechanism to rapidly generate diversity and thereby provide organisms with a competitive advantage, especially since the basal mutation rate is low (Doolittle, *Protein Science* 1:191-200, 1992).

The development of recombinant DNA methods has made it possible to study the effects of sequence transposition on protein folding, structure and function. The approach used in creating new sequences resembles that of naturally occurring pairs of proteins that are related by linear reorganization of their amino acid sequences (Cunningham, et al., *Proc. Natl. Acad. Sci. U.S.A.* 76:3218-3222, 1979; Teather & Erfle, *J. Bacteriol.* 172: 3837-3841, 1990; Schimming et al., *Eur. J. Biochem.* 204: 13-19, 1992; Yamiuchi and Minamikawa, *FEBS Lett.* 260:127-130, 1991; MacGregor et al., *FEBS Lett.* 378:263-266, 1996). The first in vitro application of this type of rearrangement to proteins was described by Goldenberg and Creighton (*J. Mol. Biol.* 165:407-413, 1983). A new N-terminus is selected at an internal site (breakpoint) of the original sequence, the new sequence having the same order of amino acids as the original from the breakpoint until it reaches an amino acid that is at or near the original C-terminus. At this point the new sequence is joined, either directly or through an additional portion of sequence (linker), to an amino acid that is at or near the original N-

7

terminus, and the new sequence continues with the same sequence as the original until it reaches a point that is at or near the amino acid that was N-terminal to the breakpoint site of the original sequence, this residue forming the new C-terminus of the chain.

This approach has been applied to proteins which range in size from 58 to 462 amino acids (Goldenberg & Creighton, *J. Mol. Biol.* 165:407-413, 1983; Li & Coffino, *Mol. Cell. Biol.* 13:2377-2383, 1993). The proteins examined have represented a broad range of structural classes, including proteins that contain predominantly α -helix (interleukin-4; Kreitman et al., *Cytokine* 7:311-318, 1995), β -sheet (interleukin-1; Horlick et al., *Protein Eng.* 5:427-431, 1992), or mixtures of the two (yeast phosphoribosyl anthranilate isomerase; Luger et al., *Science* 243:206-210, 1989). Broad categories of protein function are represented in these sequence reorganization studies:

20 Enzymes

- | | |
|------------------------------------|--|
| T4 lysozyme | Zhang et al., <i>Biochemistry</i> 32:12311-12318 (1993); Zhang et al., <i>Nature Struct. Biol.</i> 1:434-438 (1995) |
| dihydrofolate reductase | Buchwalder et al., <i>Biochemistry</i> 31:1621-1630 (1994); Protasova et al., <i>Prot. Eng.</i> 7:1373-1377 (1995) |
| ribonuclease T1 | Mullins et al., <i>J. Am. Chem. Soc.</i> 116:5529-5533 (1994); Garrett et al., <i>Protein Science</i> 5:204-211 (1996) |
| <i>Bacillus</i> β -glucanase | Hahn et al., <i>Proc. Natl. Acad. Sci. U.S.A.</i> 91:10417-10421 (1994) |

- | | | |
|----|---|---|
| | aspartate
transcarbamoylase | Yang & Schachman, <i>Proc. Natl. Acad.
Sci. U.S.A.</i> 90 :11980-11984 (1993) |
| 5 | phosphoribosyl
anthranilate
isomerase | Luger et al., <i>Science</i> 243 :206-210
(1989); Luger et al., <i>Prot. Eng.</i>
3 :249-258 (1990) |
| 10 | pepsin/pepsinogen | Lin et al., <i>Protein Science</i> 4 :159-
166 (1995) |
| | glyceraldehyde-3-
phosphate dehydro-
genase | Vignais et al., <i>Protein Science</i>
4 :994-1000 (1995) |
| 15 | ornithine
decarboxylase | Li & Coffino, <i>Mol. Cell. Biol.</i>
13 :2377-2383 (1993) |
| 20 | yeast
phosphoglycerate
dehydrogenase | Ritco-Vonsovici et al., <i>Biochemistry</i>
34 :16543-16551 (1995) |
| | Enzyme Inhibitor | |
| 25 | basic pancreatic
trypsin inhibitor | Goldenberg & Creighton, <i>J. Mol.
Biol.</i> 165 :407-413 (1983) |
| | Cytokines | |
| 30 | interleukin-1 β | Horlick et al., <i>Protein Eng.</i> 5 :427-
431 (1992) |
| | interleukin-4 | Kreitman et al., <i>Cytokine</i> 7 :311-
318 (1995) |
| 35 | Tyrosine Kinase
Recognition Domain | |

g

α -spectrin SH3 domain Viguera, et al., *J. Mol. Biol.* **247**:670-681 (1995)

Transmembrane

5 **Protein**

omp A Koebnik & Krämer, *J. Mol. Biol.* **250**:617-626 (1995)

10 **Chimeric Protein**

interleukin-4-
Pseudomonas
exotoxin fusion
15 molecule Kreitman et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:6889-6893 (1994).

The results of these studies have been highly variable. In many cases substantially lower activity, solubility or thermodynamic stability were observed (*E. coli* dihydrofolate reductase, aspartate transcarbamoylase, phosphoribosyl anthranilate isomerase, glyceraldehyde-3-phosphate dehydrogenase, ornithine decarboxylase, omp A, yeast phosphoglycerate dehydrogenase). In other cases, the sequence rearranged protein appeared to have many nearly identical properties as its natural counterpart (basic pancreatic trypsin inhibitor, T4 lysozyme, ribonuclease T1, *Bacillus* β -glucanase, interleukin-1 β , α -spectrin SH3 domain, pepsinogen, interleukin-4). In exceptional cases, an unexpected improvement over some properties of the natural sequence was observed, e.g., the solubility and refolding rate for rearranged α -spectrin SH3 domain sequences, and the receptor affinity and anti-tumor activity of transposed interleukin-4-Pseudomonas exotoxin fusion molecule (Kreitman et al., *Proc. Natl. Acad. Sci. U.S.A.* **91**:6889-6893, 1994; Kreitman et al., *Cancer Res.* **55**:3357-3363, 1995).

The primary motivation for these types of studies has been to study the role of short-range and long-range

10

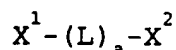
interactions in protein folding and stability. Sequence rearrangements of this type convert a subset of interactions that are long-range in the original sequence into short-range interactions in the new sequence, and vice versa. The fact that many of these sequence rearrangements are able to attain a conformation with at least some activity is persuasive evidence that protein folding occurs by multiple folding pathways (Viguera, et al., *J. Mol. Biol.* **247**:670-681, 1995). In the case of the SH3 domain of α -spectrin, choosing new termini at locations that corresponded to β -hairpin turns resulted in proteins with slightly less stability, but which were nevertheless able to fold.

The positions of the internal breakpoints used in the studies cited here are found exclusively on the surface of proteins, and are distributed throughout the linear sequence without any obvious bias towards the ends or the middle (the variation in the relative distance from the original N-terminus to the breakpoint is ca. 10 to 80% of the total sequence length). The linkers connecting the original N- and C-termini in these studies have ranged from 0 to 9 residues. In one case (Yang & Schachman, *Proc. Natl. Acad. Sci. U.S.A.* **90**:11980-11984, 1993), a portion of sequence has been deleted from the original C-terminal segment, and the connection made from the truncated C-terminus to the original N-terminus. Flexible hydrophilic residues such as Gly and Ser are frequently used in the linkers. Viguera, et al. (*J. Mol. Biol.* **247**:670-681, 1995) compared joining the original N- and C-termini with 3- or 4-residue linkers; the 3-residue linker was less thermodynamically stable. Protasova et al. (*Protein Eng.* **7**:1373-1377, 1994) used 3- or 5-residue linkers in connecting the original N-termini of *E. coli* dihydrofolate reductase; only the 3-residue linker produced protein in good yield.

//

Summary of the Invention

The modified human EPO receptor agonists of the
 5 present invention can be represented by the Formula:



wherein;

10 a is 0 or 1;

X¹ is a peptide comprising an amino acid
 sequence corresponding to the sequence of residues n+1
 through J;

X² is a peptide comprising an amino acid
 15 sequence corresponding to the sequence of residues 1
 through n;

n is an integer ranging from 1 to J-1; and
 L is a linker.

20 In the formula above the constituent amino acids
 residues of human EPO are numbered sequentially 1
 through J from the amino to the carboxyl terminus. A
 pair of adjacent amino acids within this protein may be
 numbered n and n+1 respectively where n is an integer
 25 ranging from 1 to J-1. The residue n+1 becomes the new
 N-terminus of the new EPO receptor agonist and the
 residue n becomes the new C-terminus of the new EPO
 receptor agonist.

30 The present invention relates to novel EPO receptor
 agonists polypeptides comprising a modified EPO amino
 acid sequence of the following formula:

AlaProProArgLeuIleCysAspSerArgValLeuGluArgTyrLeuLeuGluAlaLys
 35 10 20

GluAlaGluAsnIleThrThrGlyCysAlaGluHisCysSerLeuAsnGluAsnIleThr
 30 40

40 ValProAspThrLysValAsnPheTyrAlaTrpLysArgMetGluValGlyGlnGlnAla

12

50 60

ValGluValTrpGlnGlyLeuAlaLeuLeuSerGluAlaValLeuArgGlyGlnAlaLeu
70 80

5 LeuValAsnSerSerGlnProTrpGluProLeuGlnLeuHisValAspLysAlaValSer
90 100

10 GlyLeuArgSerLeuThrThrLeuLeuArgAlaLeuGlyAlaGlnLysGluAlaIleSer
110 120

ProProAspAlaAlaSerAlaAlaProLeuArgThrIleThrAlaAspThrPheArgLys
130 140

15 LeuPheArgValTyrSerAsnPheLeuArgGlyLysLeuLysLeuTyrThrGlyGluAla
150 160

CysArgThrGlyAspArg
166

20

wherein optionally 1-6 amino acids from the N-terminus
and 1-5 from the C-terminus can be deleted from said EPO
receptor agonists polypeptide;

25

wherein the N-terminus is joined to the C-terminus
directly or through a linker capable of joining the N-
terminus to the C-terminus and having new C- and N-
termini at amino acids;

23-24	48-49	111-112
24-25	50-51	112-113
25-26	51-52	113-114
26-27	52-53	114-115
27-28	53-54	115-116
28-29	54-55	116-117
29-30	55-56	117-118
30-31	56-57	118-119
31-32	57-58	119-120
32-33	77-78	120-121
33-34	78-79	121-122
34-35	79-80	122-123
35-36	80-81	123-124
36-37	81-82	124-125
37-38	82-83	125-126
38-39	84-85	126-127
40-41	85-86	127-128
41-42	86-87	128-129
43-44	87-88	129-130
44-45	88-89	131-132
45-46	108-109	respectively; and
46-47	109-110	
47-48	110-111	

13

said EPO receptor agonist polypeptide may optionally be immediately preceded by (methionine⁻¹), (alanine⁻¹) or (methionine⁻², alanine⁻¹).

5

The more preferred breakpoints at which new C-terminus and N-terminus can be made are; 23-24, 24-25, 25-26, 27-28, 28-29, 29-30, 30-31, 31-32, 32-33, 33-34, 34-35, 35-36, 36-37, 37-38, 38-39, 40-41, 41-42, 42-43, 10 52-53, 53-54, 54-55, 55-56, 77-78, 78-79, 79-80, 80-81, 81-82, 82-83, 83-84, 84-85, 85-86, 86-87, 87-88, 88-89, 109-110, 110-111, 111-112, 112-113, 113-114, 114-115, 115-116, 116-117, 117-118, 118-119, 119-120, 120-121, 121-122, 122-123, 123-124, 124-125, 125-126, 126-127, 15 127-128, 128-129, 129-130, 130-131, and 131-132.

The most preferred breakpoints at which new C-terminus and N-terminus can be made are; 23-24, 24-25, 31-32, 32-33, 37-38, 38-39, 82-83, 83-84, 85-86, 86-87, 20 87-88, 125-126, 126-127, and 131-132.

The most preferred breakpoints include glycosylation sites, non-neutralizing antibodies, proteolyte cleavage sites.

25

The EPO receptor agonists of the present invention may contain amino acid substitutions, such as those disclosed in WO 94/24160 or one or more of the glycosylation sites at Asn²⁴, Asn⁸³, and Asn¹²⁶ are 30 changed to other amino acids such as but not limited to Asp or Glu, deletions and/or insertions. It is also intended that the EPO receptor agonists of the present invention may also have amino acid deletions at either/or both the N- and C- termini of the original 35 protein and or deletions from the new N- and/or C-termini of the sequence rearranged proteins in the formulas shown above.

14

A preferred embodiment of the present invention the linker (L) joining the N-terminus to the C-terminus is a polypeptide selected from the group consisting of:

- 5 GlyGlyGlySer SEQ ID NO:123;
GlyGlyGlySerGlyGlyGlySer SEQ ID NO:124;
GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID NO:
125;
SerGlyGlySerGlyGlySer SEQ ID NO:126;
GluPheGlyAsnMet SEQ ID NO:127;
10 GluPheGlyGlyAsnMet SEQ ID NO:128;
GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:129; and
GlyGlySerAspMetAlaGly SEQ ID NO:130.

- The present invention also encompasses recombinant
- 15 human EPO receptor agonists co-administered or sequentially with one or more additional colony stimulating factors (CSF) including, cytokines, lymphokines, interleukins, hematopoietic growth factors which include but are not limited to GM-CSF, G-CSF, c-
- 20 mpl ligand (also known as TPO or MGDF), M-CSF, IL-1, IL-4, IL-2, IL-3, IL-5, IL 6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor
- 25 (SCF) also known as steel factor or c-kit ligand (herein collectively referred to as "factors"). These co-administered mixtures may be characterized by having the usual activity of both of the peptides or the mixture may be further characterized by having a biological or
- 30 physiological activity greater than simply the additive function of the presence of the EPO receptor agonists or the second colony stimulating factor alone. The co-administration may also provide an enhanced effect on the activity or an activity different from that expected
- 35 by the presence of the EPO or the second colony stimulating factor. The co-administration may also have an improved activity profile which may include reduction

of undesirable biological activities associated with native human EPO. In addition to the list above, IL-3 variants taught in WO 94/12639 and WO 94/12638 fusion protein taught in WO 95/21197, and WO 95/21254 G-CSF receptor agonists disclosed in WO 97/12977, c-mpl receptor agonists disclosed in WO 97/12978, IL-3 receptor agonists disclosed in WO 97/12979 and multi-functional receptor agonists taught in WO 97/12985 can be co-administered with the polypeptides of the present invention. As used herein "IL-3 variants" refer to IL-3 variants taught in WO 94/12639 and WO 94/12638. As used herein "fusion proteins" refer to fusion protein taught in WO 95/21197, and WO 95/21254. As used herein "G-CSF receptor agonists" refer to G-CSF receptor agonists disclosed in WO 97/12978. As used herein "c-mpl receptor agonists" refer to c-mpl receptor agonists disclosed in WO 97/12978. As used herein "IL-3 receptor agonists" refer to IL-3 receptor agonists disclosed in WO 97/12979. As used herein "multi-functional receptor agonists" refer to multi-functional receptor agonists taught in WO 97/12985.

In addition, it is envisioned that in vitro uses would include the ability to stimulate bone marrow and blood cell activation and growth before the expanded cells are infused into patients.

It is also envisioned that uses of EPO receptor agonists of the present invention would include blood banking applications, where the EPO receptor agonists are given to a patient to increase the number of red blood cells and blood products removed from the patient, prior to some medical procedure, and the blood products stored and transfused back into the patient after the medical procedure. Additionally, it is envisioned that uses of EPO receptor agonists would include giving the EPO receptor agonists to a blood donor prior to blood

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donation to increase the number of red blood cells,
thereby allowing the donor to safely give more blood.

Brief Description of the Figures

Figure 1 schematically illustrates the sequence rearrangement of a protein. The N-terminus (N) and the C-terminus (C) of the native protein are joined through a linker, or joined directly. The protein is opened at a breakpoint creating a new N-terminus (new N) and a new C-terminus (new-C) resulting in a protein with a new linear amino acid sequence. A rearranged molecule may be synthesized *de novo* as linear molecule and not go through the steps of joining the original N-terminus and the C-terminus and opening of the protein at the breakpoint.

Figure 2 shows a schematic of Method I, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined with a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to the amino acid 11 (a.a. 1- 10 are deleted) through a linker region and a new C-terminus created at amino acid 96 of the original sequence.

Figure 3 shows a schematic of Method II, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined without a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to the original N-terminus and a new C-terminus created at amino acid 96 of the original sequence.

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Figure 4 shows a schematic of Method III, for creating new proteins in which the original N-terminus and C-terminus of the native protein are joined with a linker and different N-terminus and C-terminus of the protein are created. In the example shown the sequence rearrangement results in a new gene encoding a protein with a new N-terminus created at amino acid 97 of the original protein, the original C-terminus (a.a. 174) joined to amino acid 1 through a linker region and a new C-terminus created at amino acid 96 of the original sequence.

Figure 5 shows a DNA sequence encoding human mature EPO based on the sequence of Lin et al. (PNAS 82:7580-7584, 1985).

Detailed Description of the Invention

Receptor agonists of the present invention may be useful in the treatment of diseases characterized by decreased levels of red blood cells of the hematopoietic system.

A EPO receptor agonist may be useful in the treatment or prevention of anemia. Many drugs may cause bone marrow suppression or hematopoietic deficiencies. Examples of such drugs are AZT, DDI, alkylating agents and anti-metabolites used in chemotherapy, antibiotics such as chloramphenicol, penicillin, gancyclovir, daunomycin and sulfa drugs, phenothiazones, tranquilizers such as meprobamate, analgesics such as aminopyrine and dipyrone, anti-convulsants such as phenytoin or carbamazepine, antithyroids such as propylthiouracil and methimazole and diuretics. EPO receptor agonists may be useful in preventing or treating the bone marrow suppression or hematopoietic deficiencies which often occur in patients treated with these drugs.

Hematopoietic deficiencies may also occur as a result of viral, microbial or parasitic infections and as a result of treatment for renal disease or renal failure, e.g., dialysis. The present peptide may be useful in treating such hematopoietic deficiency.

Another aspect of the present invention provides plasmid DNA vectors for use in the method of expression of these novel EPO receptor agonists. These vectors contain the novel DNA sequences described above which code for the novel polypeptides of the invention. Appropriate vectors which can transform host cells capable of expressing the EPO receptor agonists include expression vectors comprising nucleotide sequences coding for the EPO receptor agonists joined to transcriptional and translational regulatory sequences which are selected according to the host cells used.

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Vectors incorporating modified sequences as described above are included in the present invention and are useful in the production of the modified EPO receptor agonist polypeptides. The vector employed in the method
5 also contains selected regulatory sequences in operative association with the DNA coding sequences of the invention and capable of directing the replication and expression thereof in selected host cells.

As another aspect of the present invention, there
10 is provided a method for producing the novel family of human EPO receptor agonists. The method of the present invention involves culturing suitable cells or cell line, which has been transformed with a vector
15 containing a DNA sequence coding for expression of the novel EPO receptor agonist polypeptide. Suitable cells or cell lines may include various strains of bacteria such as *E. coli*, yeast, mammalian cells, or insect cells may be utilized as host cells in the method of the present invention.

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Other aspects of the present invention are methods and therapeutic compositions for treating the conditions referred to above. Such compositions comprise a
25 therapeutically effective amount of one or more of the EPO receptor agonists of the present invention in a mixture with a pharmaceutically acceptable carrier. This composition can be administered either
parenterally, intravenously or subcutaneously. When administered, the therapeutic composition for use in
30 this invention is preferably in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such a parenterally acceptable protein solution, having due regard to pH, isotonicity, stability and the like, is within the skill of the art.

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Administration will be in accordance with a dosage regimen that will be readily ascertained by the skilled,

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based on *in vivo* specific activity of the analog in comparison with human erythropoietin and based on what is now known in the art concerning the administration of human erythropoietin for inducing erythropoiesis and treating various conditions, such as anemia, in humans, including anemia in patients suffering from renal failure. Dosage of an analog of the invention may vary somewhat from individual to individual, depending on the particular analog and its specific *in vivo* activity, the route of administration, the medical condition, age, weight or sex of the patient, the patient's sensitivities to the analog or components of vehicle, and other factors which the attending physician will be capable of readily taking into account. With regard to therapeutic uses of analogs of the invention, reference is made to U.S. Patent Nos. 4,703,008 and 4,835,260; see also the chapter on (recombinant) [des-Arg¹⁶⁵]human erythropoietin at pages 591-595 of the Physicians' Desk Commercially available preparations of recombinant [des-Arg¹⁶⁵] human erythropoietin have 2,000, 3,000, 4,000 or 10,000 units of the glyco hormone per mL in preservative-free aqueous solution with 2.5 mg/mL human serum albumin, 5.8 mg/mL sodium citrate, 5.8 mg/mL NaCl, and 0.06 mg/mL citric acid, pH 6.9 (+/-0.3).

Recombinantly produced EPO has proven especially useful for the treatment of patients suffering from impaired red blood cell production (Physicians Desk Reference (PDR). 1993 edition, pp 602-605). Recombinant EPO has proven effective in treating anemia associated with chronic renal failure and HIV-Infected individuals suffering from lowered endogenous EPO levels related to therapy with Zidovudine (AZT) (See PDR, 1993 edition, at page 6002).

Modifications of the EPO protein which would improve its utility as a tool for diagnosis or treatment

of blood disorders are certainly desirable. In particular, modified forms of EPO exhibiting enhanced biological activity would be more effective and efficient than native EPO in the therapy setting when it is necessary to administer EPO to the patient, enabling administration less frequently and/or at a lower dose. Administration of reduced amounts of EPO would also presumably reduce the risk of adverse effects associated with EPO treatment, such as hypertension, seizures, headaches, etc. (See PDR, 1993 edition, at pp. 603-604). The EPO receptor agonists of the present invention may also have improved stability and hence increased half-life which would allow for the production of a non-glycosylated form of EPO in a bacterial expression system at a much lower cost. Due to its increased half-life this non-glycosylated form of EPO would have an increased in vivo activity compared to de-glycosylated EPO.

The therapeutic method and compositions may also include co-administration with other hematopoietic factors. A non-exclusive list of other appropriate hematopoietins, colony stimulating factors (CSFs) and interleukins for simultaneous or serial co-administration with the polypeptides of the present invention includes GM-CSF, G-CSF, c-mpl ligand (also known as TPO or MGDF), M-CSF, IL-1, IL-4, IL-2, IL-3, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF) also known as steel factor or c-kit ligand (herein collectively referred to as "factors"), or combinations thereof. In addition to the list above, IL-3 variants taught in WO 94/12639 and WO 94/12638 fusion protein taught in WO 95/21197, and WO 95/21254 G-CSF receptor agonists disclosed in WO 97/12977, c-mpl receptor agonists disclosed in WO 97/12978, IL-3 receptor

agonists disclosed in WO 97/12979 and multi-functional receptor agonists taught in WO 97/12985 can be co-administered with the polypeptides of the present invention.

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The EPO receptor agonists of the present invention may be useful in the mobilization of hematopoietic progenitors and stem cells in peripheral blood. Peripheral blood derived progenitors have been shown to be effective in reconstituting patients in the setting of autologous marrow transplantation.

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The EPO receptor agonists of the present invention may also be useful in the ex vivo expansion of hematopoietic progenitors. Colony stimulating factors (CSFs), such as G-CSF, have been administered alone, co-administered with other CSFs, or in combination with bone marrow transplants subsequent to high dose chemotherapy to treat the anemia, neutropenia and thrombocytopenia which are often the result of such treatment.

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Another aspect of the invention provides methods of sustaining and/or expanding hematopoietic precursor cells which includes inoculating the cells into a culture vessel which contains a culture medium that has been conditioned by exposure to a stromal cell line such as HS-5 (WO 96/02662, Roecklein and Torok-Strob, Blood 85:997-1105, 1995) that has been supplemented with a EPO receptor agonist of the present invention.

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Determination of the Linker

The length of the amino acid sequence of the linker can be selected empirically or with guidance from structural information, or by using a combination of the two approaches.

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When no structural information is available, a small series of linkers can be prepared for testing using a design whose length is varied in order to span a range from 0 to 50 Å and whose sequence is chosen in order to be consistent with surface exposure (hydrophilicity, Hopp & Woods, *Mol. Immunol.* **20**: 483-489, 1983; Kyte & Doolittle, *J. Mol. Biol.* **157**:105-132, 1982; solvent exposed surface area, Lee & Richards, *J. Mol. Biol.* **55**:379-400, 1971) and the ability to adopt the necessary conformation without deranging the configuration of the EPO receptor agonist (conformationally flexible; Karplus & Schulz, *Naturwissenschaften* **72**:212-213, (1985). Assuming an average of translation of 2.0 to 3.8 Å per residue, this would mean the length to test would be between 0 to 30 residues, with 0 to 15 residues being the preferred range. Exemplary of such an empirical series would be to construct linkers using a cassette sequence such as Gly-Gly-Gly-Ser repeated n times, where n is 1, 2, 3 or 4. Those skilled in the art will recognize that there are many such sequences that vary in length or composition that can serve as linkers with the primary consideration being that they be neither excessively long nor short (cf., Sandhu, *Critical Rev. Biotech.* **12**: 437-462, 1992); if they are too long, entropy effects will likely destabilize the three-dimensional fold, and may also make folding kinetically impractical, and if they are too short, they will likely destabilize the molecule because of torsional or steric strain.

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Those skilled in the analysis of protein structural information will recognize that using the distance between the chain ends, defined as the distance between the c-alpha carbons, can be used to define the length of the sequence to be used, or at least to limit the number of possibilities that must be tested in an empirical selection of linkers. They will also recognize that it

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is sometimes the case that the positions of the ends of the polypeptide chain are ill-defined in structural models derived from x-ray diffraction or nuclear magnetic resonance spectroscopy data, and that when true, this situation will therefore need to be taken into account in order to properly estimate the length of the linker required. From those residues whose positions are well defined are selected two residues that are close in sequence to the chain ends, and the distance between their c-alpha carbons is used to calculate an approximate length for a linker between them. Using the calculated length as a guide, linkers with a range of number of residues (calculated using 2 to 3.8Å per residue) are then selected. These linkers may be composed of the original sequence, shortened or lengthened as necessary, and when lengthened the additional residues may be chosen to be flexible and hydrophilic as described above; or optionally the original sequence may be substituted for using a series of linkers, one example being the "Gly-Gly-Gly-Ser" cassette approach mentioned above; or optionally a combination of the original sequence and new sequence having the appropriate total length may be used.

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Determination of the Amino and Carboxyl Termini of EPO Receptor Agonists

Sequences of EPO receptor agonists capable of folding to biologically active states can be prepared by appropriate selection of the beginning (amino terminus) and ending (carboxyl terminus) positions from within the original polypeptide chain while using the linker sequence as described above. Amino and carboxyl termini are selected from within a common stretch of sequence, referred to as a breakpoint region, using the guidelines described below. A novel amino acid sequence is thus generated by selecting amino and carboxyl termini from

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within the same breakpoint region. In many cases the selection of the new termini will be such that the original position of the carboxyl terminus immediately preceded that of the amino terminus. However, those skilled in the art will recognize that selections of termini anywhere within the region may function, and that these will effectively lead to either deletions or additions to the amino or carboxyl portions of the new sequence.

It is a central tenet of molecular biology that the primary amino acid sequence of a protein dictates folding to the three-dimensional structure necessary for expression of its biological function. Methods are known to those skilled in the art to obtain and interpret three-dimensional structural information using x-ray diffraction of single protein crystals or nuclear magnetic resonance spectroscopy of protein solutions. Examples of structural information that are relevant to the identification of breakpoint regions include the location and type of protein secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets, chain reversals and turns, and loops; Kabsch & Sander, *Biopolymers* 22: 2577-2637, 1983; the degree of solvent exposure of amino acid residues, the extent and type of interactions of residues with one another (Chothia, *Ann. Rev. Biochem.* 53:537-572; 1984) and the static and dynamic distribution of conformations along the polypeptide chain (Alber & Mathews, *Methods Enzymol.* 154: 511-533, 1987). In some cases additional information is known about solvent exposure of residues; one example is a site of post-translational attachment of carbohydrate which is necessarily on the surface of the protein. When experimental structural information is not available, or is not feasible to obtain, methods are also available to analyze the primary amino acid sequence in order to make predictions of protein tertiary and secondary structure, solvent accessibility

and the occurrence of turns and loops. Biochemical methods are also sometimes applicable for empirically determining surface exposure when direct structural methods are not feasible; for example, using the

5 identification of sites of chain scission following limited proteolysis in order to infer surface exposure (Gentile & Salvatore, *Eur. J. Biochem.* **218**:603-621, 1993)

Thus using either the experimentally derived structural

10 information or predictive methods (e.g., Srinivisan & Rose *Proteins: Struct., Funct. & Genetics*, **22**: 81-99, 1995) the parental amino acid sequence is inspected to classify regions according to whether or not they are integral to the maintenance of secondary and tertiary

15 structure. The occurrence of sequences within regions that are known to be involved in periodic secondary structure (alpha and 3-10 helices, parallel and anti-parallel beta sheets) are regions that should be avoided. Similarly, regions of amino acid sequence that

20 are observed or predicted to have a low degree of solvent exposure are more likely to be part of the so-called hydrophobic core of the protein and should also be avoided for selection of amino and carboxyl termini. In contrast, those regions that are known or predicted

25 to be in surface turns or loops, and especially those regions that are known not to be required for biological activity, are the preferred sites for location of the extremes of the polypeptide chain. Continuous stretches of amino acid sequence that are preferred based on the

30 above criteria are referred to as a breakpoint region.

Materials and Methods

Recombinant DNA methods

35 Unless noted otherwise, all specialty chemicals were obtained from Sigma Co., (St. Louis, MO). Restriction endonucleases and T4 DNA ligase were

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obtained from New England Biolabs (Beverly, MA) or Boehringer Mannheim (Indianapolis, IN).

Transformation of *E. coli* strains

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E. coli strains, such as DH5 α [™] (Life Technologies, Gaithersburg, MD) and TG1 (Amersham Corp., Arlington Heights, IL) are used for transformation of ligation reactions and are the source of plasmid DNA for

10 transfecting mammalian cells. *E. coli* strains, such as MON105 and JM101, can be used for expressing the EPO receptor agonist of the present invention in the cytoplasm or periplasmic space.

15 MON105 ATCC#55204: F⁻, lamda⁻, IN(rrnD, rrE)1, rpoD⁺, rpoH358

DH5 α [™]: F⁻, phi80dlacZdeltaM15, delta(lacZYA-argF)U169, deoR, recA1, endA1, hsdR17(rk⁻,mk⁺), phoA, supE44lamda⁻,
20 thi-1, gyrA96, relA1

TG1: delta(lac-pro), supE, thi-1, hsdD5/F'(traD36, proA+B⁺, lacIq, lacZdeltaM15)

25 DH5 α [™] Subcloning efficiency cells are purchased as competent cells and are ready for transformation using the manufacturer's protocol, while both *E. coli* strains TG1 and MON105 are rendered competent to take up DNA using a CaCl₂ method. Typically, 20 to 50 mL of cells
30 are grown in LB medium (1% Bacto-tryptone, 0.5% Bacto-yeast extract, 150 mM NaCl) to a density of approximately 1.0 optical density unit at 600 nanometers (OD₆₀₀) as measured by a Baush & Lomb Spectronic spectrophotometer (Rochester, NY). The cells are
35 collected by centrifugation and resuspended in one-fifth culture volume of CaCl₂ solution (50 mM CaCl₂, 10 mM Tris-Cl, pH7.4) and are held at 4°C for 30 minutes. The

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cells are again collected by centrifugation and resuspended in one-tenth culture volume of CaCl_2 solution. Ligated DNA is added to 0.2mL of these cells, and the samples are held at 4°C for 1 hour. The samples are shifted to 42°C for two minutes and 1mL of LB is added prior to shaking the samples at 37°C for one hour. Cells from these samples are spread on plates (LB medium plus 1.5% Bacto-agar) containing either ampicillin (100 micrograms/mL, ug/mL) when selecting for ampicillin-resistant transformants, or spectinomycin (75 ug/mL) when selecting for spectinomycin-resistant transformants. The plates are incubated overnight at 37°C. Single colonies are picked, grown in LB supplemented with appropriate antibiotic for 6-16 hours at 37°C with shaking. Colonies are picked and inoculated into LB plus appropriate antibiotic (100 ug/mL ampicillin or 75 ug/mL spectinomycin) and are grown at 37°C while shaking. Before harvesting the cultures, 1 ul of cells are analyzed by PCR for the presence of a EPO receptor agonist gene. The PCR is carried out using a combination of primers that anneal to the EPO receptor agonist gene and/or vector. After the PCR is complete, loading dye is added to the sample followed by electrophoresis as described earlier. A gene has been ligated to the vector when a PCR product of the expected size is observed.

Methods for creation of genes with new N-terminus/C-terminus

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Method I. Creation of genes with new N-terminus/C-terminus which contain a linker region.

Genes with new N-terminus/C-terminus which contain a linker region separating the original C-terminus and N-terminus can be made essentially following the method described in L. S. Mullins, et al *J. Am. Chem. Soc.* **116**,

5529-5533 (1994). Multiple steps of polymerase chain reaction (PCR) amplifications are used to rearrange the DNA sequence encoding the primary amino acid sequence of the protein. The steps are illustrated in Figure 2.

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In the first step, the primer set ("new start" and "linker start") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Start") that contains the sequence encoding the new N-terminal portion of the new protein followed by the linker that connects the C-terminal and N-terminal ends of the original protein. In the second step, the primer set ("new stop" and "linker stop") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Stop") that encodes the same linker as used above, followed by the new C-terminal portion of the new protein. The "new start" and "new stop" primers are designed to include the appropriate restriction enzyme recognition sites which allow cloning of the new gene into expression plasmids. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit is used. A 100 ul reaction contains 100 pmole of each primer and one ug of template DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM MgCl₂. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT).

"Fragment Start" and "Fragment Stop", which have complementary sequence in the linker region and the coding sequence for the two amino acids on both sides of the linker, are joined together in a third PCR step to make the full-length gene encoding the new protein. The

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DNA fragments "Fragment Start" and "Fragment Stop" are resolved on a 1% TAE gel, stained with ethidium bromide and isolated using a Qiaex Gel Extraction kit (Qiagen). These fragments are combined in equimolar quantities, heated at 70°C for ten minutes and slow cooled to allow annealing through their shared sequence in "linker start" and "linker stop". In the third PCR step, primers "new start" and "new stop" are added to the annealed fragments to create and amplify the full-length new N-terminus/C-terminus gene. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 60°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit is used. A 100 ul reaction contains 100 pmole of each primer and approximately 0.5 ug of DNA; and 1x PCR buffer, 200 uM dGTP, 200 uM dATP, 200 uM dTTP, 200 uM dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM MgCl₂. PCR reactions are purified using a Wizard PCR Preps kit (Promega).

Method II. Creation of genes with new N-terminus/C-terminus without a linker region.

New N-terminus/C-terminus genes without a linker joining the original N-terminus and C-terminus can be made using two steps of PCR amplification and a blunt end ligation. The steps are illustrated in Figure 3. In the first step, the primer set ("new start" and "P-bl start") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Start") that contains the sequence encoding the new N-terminal portion of the new protein. In the second step, the primer set ("new stop" and "P-bl stop") is used to create and amplify, from the original gene sequence, the DNA fragment ("Fragment Stop") that contains the sequence encoding the new C-terminal portion of the new

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protein. The "new start" and "new stop" primers are designed to include appropriate restriction sites which allow cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for 45 seconds and 72°C extension for 45 seconds. Deep Vent polymerase (New England Biolabs) is used to reduce the occurrence of overhangs in conditions recommended by the manufacturer. The "P-bl start" and "P-bl stop" primers are phosphorylated at the 5' end to aid in the subsequent blunt end ligation of "Fragment Start" and "Fragment Stop" to each other. A 100 ul reaction contained 150 pmole of each primer and one ug of template DNA; and 1x Vent buffer (New England Biolabs), 300 uM dGTP, 300 uM dATP, 300 uM dTTP, 300 uM dCTP, and 1 unit Deep Vent polymerase. PCR reactions are performed in a Model 480 DNA thermal cycler (Perkin Elmer Corporation, Norwalk, CT). PCR reaction products are purified using a Wizard PCR Preps kit (Promega).

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The primers are designed to include appropriate restriction enzyme recognition sites which allow for the cloning of the new gene into expression vectors. Typically "Fragment Start" is designed to create a NcoI restriction site, and "Fragment Stop" is designed to create a HindIII restriction site. Restriction digest reactions are purified using a Magic DNA Clean-up System kit (Promega). Fragments Start and Stop are resolved on a 1% TAE gel, stained with ethidium bromide and isolated using a Qiaex Gel Extraction kit (Qiagen). These fragments are combined with and annealed to the ends of the ~ 3800 base pair NcoI/HindIII vector fragment of pMON3934 by heating at 50°C for ten minutes and allowed to slow cool. The three fragments are ligated together using T4 DNA ligase (Boehringer Mannheim). The result is a plasmid containing the full-length new N-terminus/C-terminus gene. A portion of the ligation reaction is

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used to transform *E. coli* strain DH5 α cells (Life Technologies, Gaithersburg, MD). Plasmid DNA is purified and sequence confirmed as below.

5 Method III. Creation of new N-terminus/C-terminus genes by tandem-duplication method

New N-terminus/C-terminus genes can be made based on the method described in R. A. Horlick, et al *Protein*
10 *Eng.* 5:427-431 (1992). Polymerase chain reaction (PCR) amplification of the new N-terminus/C-terminus genes is performed using a tandemly duplicated template DNA. The steps are illustrated in Figure 4.

15 The tandemly-duplicated template DNA is created by cloning and contains two copies of the gene separated by DNA sequence encoding a linker connecting the original C- and N-terminal ends of the two copies of the gene. Specific primer sets are used to create and amplify a
20 full-length new N terminus/C-terminus gene from the tandemly-duplicated template DNA. These primers are designed to include appropriate restriction sites which allow for the cloning of the new gene into expression vectors. Typical PCR conditions are one cycle 95°C
25 melting for two minutes; 25 cycles 94°C denaturation for one minute, 50°C annealing for one minute and 72°C extension for one minute; plus one cycle 72°C extension for seven minutes. A Perkin Elmer GeneAmp PCR Core Reagents kit (Perkin Elmer Corporation, Norwalk, CT) is
30 used. A 100 μ l reaction contains 100 pmole of each primer and one μ g of template DNA; and 1x PCR buffer, 200 μ M dGTP, 200 μ M dATP, 200 μ M dTTP, 200 μ M dCTP, 2.5 units AmpliTaq DNA polymerase and 2 mM MgCl₂. PCR reactions are performed in a Model 480 DNA thermal
35 cyclor (Perkin Elmer Corporation, Norwalk, CT). PCR reactions are purified using a Wizard PCR Preps kit (Promega).

DNA isolation and characterization

Plasmid DNA can be isolated by a number of
5 different methods and using commercially available kits
known to those skilled in the art. A few such methods
are shown herein. Plasmid DNA is isolated using the
Promega Wizard™ Miniprep kit (Madison, WI), the Qiagen
QIAwell Plasmid isolation kits (Chatsworth, CA) or
10 Qiagen Plasmid Midi kit. These kits follow the same
general procedure for plasmid DNA isolation. Briefly,
cells are pelleted by centrifugation (5000 x g), plasmid
DNA released with sequential NaOH/acid treatment, and
cellular debris is removed by centrifugation (10000 x
15 g). The supernatant (containing the plasmid DNA) is
loaded onto a column containing a DNA-binding resin, the
column is washed, and plasmid DNA eluted with TE. After
screening for the colonies with the plasmid of interest,
the *E. coli* cells are inoculated into 50-100 mLs of LB
20 plus appropriate antibiotic for overnight growth at 37°C
in an air incubator while shaking. The purified plasmid
DNA is used for DNA sequencing, further restriction
enzyme digestion, additional subcloning of DNA fragments
and transfection into mammalian, *E. coli* or other cells.

25 Sequence confirmation.

Purified plasmid DNA is resuspended in dH₂O and
quantitated by measuring the absorbance at 260/280 nm in
30 a Bausch and Lomb Spectronic 601 UV spectrometer. DNA
samples are sequenced using ABI PRISM™ DyeDeoxy™
terminator sequencing chemistry (Applied Biosystems
Division of Perkin Elmer Corporation, Lincoln City, CA)
kits (Part Number 401388 or 402078) according to the
35 manufacturers suggested protocol usually modified by the
addition of 5% DMSO to the sequencing mixture.
Sequencing reactions are performed in a Model 480 DNA
thermal cycler (Perkin Elmer Corporation, Norwalk, CT)

following the recommended amplification conditions. Samples are purified to remove excess dye terminators with Centri-Sep™ spin columns (Princeton Separations, Adelphia, NJ) and lyophilized. Fluorescent dye labeled sequencing reactions are resuspended in deionized formamide, and sequenced on denaturing 4.75% polyacrylamide-8M urea gels using an ABI Model 373A automated DNA sequencer. Overlapping DNA sequence fragments are analyzed and assembled into master DNA contigs using Sequencher v2.1 DNA analysis software (Gene Codes Corporation, Ann Arbor, MI).

Expression of EPO receptor agonists in mammalian cells

15 Mammalian Cell Transfection/Production of Conditioned Media

The BHK-21 cell line can be obtained from the ATCC (Rockville, MD). The cells are cultured in Dulbecco's modified Eagle media (DMEM/high-glucose), supplemented to 2mM (mM) L-glutamine and 10% fetal bovine serum (FBS). This formulation is designated BHK growth media. Selective media is BHK growth media supplemented with 453 units/mL hygromycin B (Calbiochem, San Diego, CA). The BHK-21 cell line was previously stably transfected with the HSV transactivating protein VP16, which transactivates the IE110 promoter found on the plasmid pMON3359 (See Hippenmeyer et al., *Bio/Technology*, pp.1037-1041, 1993). The VP16 protein drives expression of genes inserted behind the IE110 promoter. BHK-21 cells expressing the transactivating protein VP16 are designated BHK-VP16. The plasmid pMON1118 (See Highkin et al., *Poultry Sci.*, 70: 970-981, 1991) expresses the hygromycin resistance gene from the SV40 promoter. A similar plasmid is available from ATCC, pSV2-hph.

BHK-VP16 cells are seeded into a 60 millimeter (mm) tissue culture dish at 3×10^5 cells per dish 24 hours

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prior to transfection. Cells are transfected for 16 hours in 3 mL of "OPTIMEM"™ (Gibco-BRL, Gaithersburg, MD) containing 10 ug of plasmid DNA containing the gene of interest, 3 ug hygromycin resistance plasmid, pMON1118, and 80 ug of Gibco-BRL "LIPOFECTAMINE"™ per dish. The media is subsequently aspirated and replaced with 3 mL of growth media. At 48 hours post-transfection, media from each dish is collected and assayed for activity (transient conditioned media). The cells are removed from the dish by trypsin-EDTA, diluted 1:10 and transferred to 100 mm tissue culture dishes containing 10 mL of selective media. After approximately 7 days in selective media, resistant cells grow into colonies several millimeters in diameter. The colonies are removed from the dish with filter paper (cut to approximately the same size as the colonies and soaked in trypsin/EDTA) and transferred to individual wells of a 24 well plate containing 1 mL of selective media. After the clones are grown to confluence, the conditioned media is re-assayed, and positive clones are expanded into growth media.

Expression of EPO receptor agonists in *E. coli*

E. coli strain MON105 or JM101 harboring the plasmid of interest are grown at 37°C in M9 plus casamino acids medium with shaking in a air incubator Model G25 from New Brunswick Scientific (Edison, New Jersey). Growth is monitored at OD600 until it reaches a value of 1, at which time nalidixic acid (10 milligrams/mL) in 0.1 N NaOH is added to a final concentration of 50 µg/mL. The cultures are then shaken at 37°C for three to four additional hours. A high degree of aeration is maintained throughout culture period in order to achieve maximal production of the desired gene product. The cells are examined under a light microscope for the presence of inclusion bodies

- (IB). One mL aliquots of the culture are removed for analysis of protein content by boiling the pelleted cells, treating them with reducing buffer and electrophoresis via SDS-PAGE (see Maniatis et al. 5 Molecular Cloning: A Laboratory Manual, 1982). The culture is centrifuged (5000 x g) to pellet the cells.

- Additional strategies for achieving high-level expression of genes in *E. coli* can be found in Savvas, 10 C.M. (*Microbiological Reviews* 60;512-538, 1996).

- Inclusion Body preparation, Extraction, Refolding, Dialysis, DEAE Chromatography, and Characterization of
15 the EPO receptor agonists which accumulate as inclusion bodies in *E. coli*.

Isolation of Inclusion Bodies:

- 20 The cell pellet from a 330 mL *E. coli* culture is resuspended in 15 mL of sonication buffer (10 mM 2-amino-2-(hydroxymethyl) 1,3-propanediol hydrochloride (Tris-HCl), pH 8.0 + 1 mM ethylenediaminetetraacetic acid (EDTA)). These resuspended cells are sonicated
25 using the microtip probe of a Sonicator Cell Disruptor (Model W-375, Heat Systems-Ultrasonics, Inc., Farmingdale, New York). Three rounds of sonication in sonication buffer followed by centrifugation are employed to disrupt the cells and wash the inclusion
30 bodies (IB). The first round of sonication is a 3 minute burst followed by a 1 minute burst, and the final two rounds of sonication are for 1 minute each.

- Extraction and refolding of proteins from inclusion body
35 pellets:

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Following the final centrifugation step, the IB pellet is resuspended in 10 mL of 50 mM Tris-HCl, pH 9.5, 8 M urea and 5 mM dithiothreitol (DTT) and stirred at room temperature for approximately 45 minutes to
5 allow for denaturation of the expressed protein.

The extraction solution is transferred to a beaker containing 70 mL of 5mM Tris-HCl, pH 9.5 and 2.3 M urea and gently stirred while exposed to air at 4°C for 18 to 48 hours to allow the proteins to refold. Refolding is
10 monitored by analysis on a Vydac (Hesperia, Ca.) C18 reversed phase high pressure liquid chromatography (RP-HPLC) column (0.46x25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid (TFA), is employed to monitor the refold. This gradient
15 is developed over 30 minutes at a flow rate of 1.5 mL per minute. Denatured proteins generally elute later in the gradient than the refolded proteins.

Purification:

20

Following the refold, contaminating *E. coli* proteins are removed by acid precipitation. The pH of the refold solution is titrated to between pH 5.0 and pH 5.2 using 15% (v/v) acetic acid (HOAc). This solution
25 is stirred at 4°C for 2 hours and then centrifuged for 20 minutes at 12,000 x g to pellet any insoluble protein.

The supernatant from the acid precipitation step is dialyzed using a Spectra/Por 3 membrane with a molecular weight cut off (MWCO) of 3,500 daltons. The dialysis is
30 against 2 changes of 4 liters (a 50-fold excess) of 10mM Tris-HCl, pH 8.0 for a total of 18 hours. Dialysis lowers the sample conductivity and removes urea prior to DEAE chromatography. The sample is then centrifuged (20
35 minutes at 12,000 x g) to pellet any insoluble protein following dialysis.

A Bio-Rad Bio-Scale DEAE2 column (7 x 52 mm) is used for ion exchange chromatography. The column is equilibrated in a buffer containing 10mM Tris-HCl, pH 8.0. The protein is eluted using a 0-to-500 mM sodium chloride (NaCl) gradient, in equilibration buffer, over 45 column volumes. A flow rate of 1 mL per minute is used throughout the run. Column fractions (2 mL per fraction) are collected across the gradient and analyzed by RP HPLC on a Vydac (Hesperia, Ca.) C18 column (0.46 x 25 cm). A linear gradient of 40% to 65% acetonitrile, containing 0.1% trifluoroacetic acid (TFA), is employed. This gradient is developed over 30 minutes at a flow rate of 1.5 mL per minute. Pooled fractions are then dialyzed against 2 changes of 4 liters (50-to-500-fold excess) of 10 mM ammonium acetate (NH₄Ac), pH 4.0 for a total of 18 hours. Dialysis is performed using a Spectra/Por 3 membrane with a MWCO of 3,500 daltons. Finally, the sample is sterile filtered using a 0.22µm syringe filter (µStar LB syringe filter, Costar, Cambridge, Ma.), and stored at 4°C.

In some cases the folded proteins can be affinity purified using affinity reagents such as mAbs or receptor subunits attached to a suitable matrix. Alternatively, (or in addition) purification can be accomplished using any of a variety of chromatographic methods such as: ion exchange, gel filtration or hydrophobic chromatography or reversed phase HPLC.

These and other protein purification methods are described in detail in Methods in Enzymology, Volume 182 'Guide to Protein Purification' edited by Murray Deutscher, Academic Press, San Diego, CA (1990).

Protein Characterization:

The purified protein is analyzed by RP-HPLC, electrospray mass spectrometry, and SDS-PAGE. The

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protein quantitation is done by amino acid composition, RP-HPLC, and Bradford protein determination. In some cases tryptic peptide mapping is performed in conjunction with electrospray mass spectrometry to confirm the identity of the protein.

Methylcellulose Assay

This assay reflects the ability of colony stimulating factors to stimulate normal bone marrow cells to produce different types of hematopoietic colonies in vitro (Bradley et al., *Aust. Exp Biol. Sci.* 44:287-300, 1966), Pluznik et al., *J. Cell Comp. Physio* 66:319-324, 1965).

15

Methods

Approximately 30 mL of fresh, normal, healthy bone marrow aspirate are obtained from individuals following informed consent. Under sterile conditions samples are diluted 1:5 with a 1X PBS (#14040.059 Life Technologies, Gaithersburg, MD.) solution in a 50 mL conical tube (#25339-50 Corning, Corning MD). Ficoll (Histopaque 1077 Sigma H-8889) is layered under the diluted sample and centrifuged, 300 x g for 30 min. The mononuclear cell band is removed and washed two times in 1X PBS and once with 1% BSA PBS (CellPro Co., Bothel, WA). Mononuclear cells are counted and CD34+ cells are selected using the Ceparate LC (CD34) Kit (CellPro Co., Bothel, WA) column. This fractionation is performed since all stem and progenitor cells within the bone marrow display CD34 surface antigen.

Cultures are set up in triplicate with a final volume of 1.0 mL in a 35 X 10 mm petri dish (Nunc#174926). Culture medium is purchased from Terry Fox Labs. (HCC-4230 medium (Terry Fox Labs, Vancouver, B.C., Canada) and erythropoietin (Amgen, Thousand Oaks, CA.) is added

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to the culture media. 3,000-10,000 CD34+ cells are added per dish. EPO receptor agonist proteins, in conditioned media from transfected mammalian cells or purified from conditioned media from transfected mammalian cells or *E. coli*, are added to give final concentrations ranging from .001 nM to 10 nM. Cultures are resuspended using a 3cc syringe and 1.0 mL is dispensed per dish. Control (baseline response) cultures received no colony stimulating factors.

Positive control cultures received conditioned media (PHA stimulated human cells: Terry Fox Lab. H2400). Cultures are incubated at 37°C, 5% CO₂ in humidified air.

Hematopoietic colonies which are defined as greater than 50 cells are counted on the day of peak response (days 10-11) using a Nikon inverted phase microscope with a 40x objective combination. Groups of cells containing fewer than 50 cells are referred to as clusters. Alternatively colonies can be identified by spreading the colonies on a slide and stained or they can be picked, resuspended and spun onto cytopsin slides for staining.

Human Cord Blood Hematopoietic Growth Factor Assays

Bone marrow cells are traditionally used for in vitro assays of hematopoietic colony stimulating factor (CSF) activity. However, human bone marrow is not always available, and there is considerable variability between donors. Umbilical cord blood is comparable to bone marrow as a source of hematopoietic stem cells and progenitors (Broxmeyer et al., *PNAS USA* 89:4109-113, 1992; Mayani et al., *Blood* 81:3252-3258, 1993). In contrast to bone marrow, cord blood is more readily available on a regular basis. There is also a potential to reduce assay variability by pooling cells obtained fresh from several donors, or to create a bank of

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cryopreserved cells for this purpose. By modifying the culture conditions, and/or analyzing for lineage specific markers, it is possible to assay specifically for burst forming colonies (BFU-E) activity.

Methods

Mononuclear cells (MNC) are isolated from cord blood within 24 hr. of collection, using a standard density gradient (1.077 g/mL Histopaque). Cord blood MNC have been further enriched for stem cells and progenitors by several procedures, including immunomagnetic selection for CD14-, CD34+ cells; panning for SBA-, CD34+ fraction using coated flasks from Applied Immune Science (Santa Clara, CA); and CD34+ selection using a CellPro (Bothell, WA) avidin column. Either freshly isolated or cryopreserved CD34+ cell enriched fractions are used for the assay. Duplicate cultures for each serial dilution of sample (concentration range from 1 pM to 1204 pM) are prepared with 1×10^4 cells in 1ml of 0.9% methylcellulose containing medium without additional growth factors (Methocult H4230 from Stem Cell Technologies, Vancouver, BC.). After culturing for 7-9 days, colonies containing >30 cells are counted.

Transfected cell lines:

Cell lines, such as BHK or the murine pro B cell line Baf/3, can be transfected with a colony stimulating factor receptor, such as the human EPO receptor which the cell line does not have. These transfected cell lines can be used to determine the cell proliferative activity and/or receptor binding.

EXAMPLE 1

Genes encoding the sequence rearranged EPO ligands can be constructed by any one of the methods described herein or by other recombinant methods known to those

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skilled in the art. For the purpose of this example, the site of permutation is between residues 131(Arg) and 132(Thr) of EPO. This is a site which is susceptible to proteolytic cleavage, thereby indicating surface exposure with a relatively high degree of flexibility.

In this example a new N-terminus and a new C-terminus is created without a linker joining the original termini. This is done, as described in Method II, in 2 steps of PCR and a blunt end ligation.

In the first PCR step, using a vector containing the DNA sequence of SEQ ID NO:120 as the template, and the primers "new start" and "blunt start", a DNA fragment is created which encodes the new N-terminus. This fragment is termed "fragment start". The sequence underlined in the new start primer is the NcoI restriction site.

New start primer = gcgcgcCCATGGACAATCACTGCTGAC SEQ ID NO:131
Blunt start primer = TCTGTCCCCTGTCCT SEQ ID NO:132

In the second PCR step, using a vector containing the DNA sequence of SEQ ID NO:120 as the template, and the primers "new stop" and "blunt stop" create a DNA fragment which encodes the new C-terminus. This fragment is termed "fragment stop". The sequence underlined in the new stop primer is the HindIII restriction site.

New stop primer = gcgcgcAAGCTTATTATCGGAGTGGAGCAGCTGAGGCCGCATC SEQ ID NO:133

Blunt end primer = GCCCCACCAAGCCTCATCTGT SEQ ID NO:134

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In the ligation step, the two fragments created in the two PCR reactions are ligated together, digested with NcoI and HindIII and cloned into an expression vector. The clones are screened by restriction analysis and DNA
5 sequenced to confirm the proper sequence. The primers can be designed to create restriction sites other than NcoI and HindIII to clone into other expression vectors.

10

EXAMPLE 2

The sequence rearranged EPO receptor agonists of the present invention can be assayed for bioactivity by the methods described herein or by other assays known to
15 those skilled in the art.

Additional techniques for the construction of the variant genes, recombinant protein expression, protein purification, protein characterization, biological
20 activity determination can be found in WO 94/12639, WO 94/12638, WO 95/20976, WO 95/21197, WO 95/20977, WO 95/21254 which are hereby incorporated by reference in their entirety.

25 All references, patents or applications cited herein are incorporated by reference in their entirety as if written herein.

Various other examples will be apparent to the
30 person skilled in the art after reading the present disclosure without departing from the spirit and scope of the invention. It is intended that all such other examples be included within the scope of the appended claims.

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SEQUENCE LISTING

(1) GENERAL INFORMATION

- (i) APPLICANT: G. D. Searle and Company
- (ii) TITLE OF THE INVENTION: Novel Erythropoietin Receptor Agonists
- (iii) NUMBER OF SEQUENCES: 134
- (iv) CORRESPONDENCE ADDRESS:
 (A) ADDRESSEE: G. D. Searle & Co.
 (B) STREET: P.O. Box 5110
 (C) CITY: Chicago
 (D) STATE: IL
 (E) COUNTRY: U. S. A.
 (F) ZIP: 60680
- (v) COMPUTER READABLE FORM:
 (A) MEDIUM TYPE: Diskette
 (B) COMPUTER: IBM Compatible
 (C) OPERATING SYSTEM: DOS
 (D) SOFTWARE: FastSEQ for Windows Version 2.0
- (vi) CURRENT APPLICATION DATA:
 (A) APPLICATION NUMBER:
 (B) FILING DATE: 21-OCT-1997
 (C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
 (A) APPLICATION NUMBER: 60/034,044
 (B) FILING DATE: 25-OCT-1996
- (viii) ATTORNEY/AGENT INFORMATION:
 (A) NAME: Bennett, Dennis A
 (B) REGISTRATION NUMBER: 34,547
 (C) REFERENCE/DOCKET NUMBER: 2991/1
- (ix) TELECOMMUNICATION INFORMATION:
 (A) TELEPHONE: 314-737-6986
 (B) TELEFAX: 314-737-6972
 (C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```

Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile
 1           5           10           15
Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
          20           25           30
Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
          35           40           45
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
          50           55           60
Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
          65           70           75           80
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile
          85           90           95
Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala
          100          105          110
Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly
          115          120          125

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Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly
 130          135          140
Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu
145          150          155          160
Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu
          165          170

```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr
 1          5          10          15
Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
          20          25          30
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
          35          40          45
Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp
          50          55          60
Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
65          70          75          80
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
          85          90          95
Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp
          100          105          110
Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys
          115          120          125
Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly
          130          135          140
Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg
145          150          155          160
Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
          165          170

```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```

Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val
 1          5          10          15
Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly
          20          25          30
Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala
          35          40          45
Val Leu Arg Gly Gln Ala Leu Val Asn Ser Ser Gln Pro Trp Glu
          50          55          60
Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu
65          70          75          80
Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro
          85          90          95
Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr
          100          105          110
Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu
          115          120          125
Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly
          130          135          140
Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr
145          150          155          160
Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile
          165          170

```

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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
 1      5      10      15
Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln
 20      25      30
Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Ser Glu Ala Val
 35      40      45
Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro
 50      55      60
Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr
 65      70      75      80
Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro
 85      90      95
Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe
100      105      110
Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys
115      120      125
Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser
130      135      140
Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
145      150      155      160
Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr
165      170

```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```

Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp
 1      5      10      15
Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln
 20      25      30
Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu
 35      40      45
Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu
 50      55      60
Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr
 65      70      75      80
Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp
 85      90      95
Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg
100      105      110
Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu
115      120      125
Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala
130      135      140
Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu
145      150      155      160
Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr
165      170

```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```

Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr
 1      5      10      15
Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala
 20      25      30
Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg
 35      40      45
Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln
 50      55      60
Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu
 65      70      75      80
Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala
 85      90      95
Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys
100      105      110
Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr
115      120      125
Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro
130      135      140
Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu
145      150      155      160
Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly
165      170

```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```

Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys
 1      5      10      15
Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val
 20      25      30
Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly
 35      40      45
Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu
 50      55      60
His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu
 65      70      75      80
Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala
 85      90      95
Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu
100      105      110
Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr
115      120      125
Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro
130      135      140
Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala
145      150      155      160
Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys
165      170

```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```

Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val
 1      5      10      15

```

```

Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu
    20          25          30
Val Trp Gln Gly Leu Ala Leu Ser Glu Ala Val Leu Arg Gly Gln
    35          40          45
Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His
    50          55          60
Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg
    65          70          75          80
Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser
    85          90          95
Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe
    100          105          110
Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly
    115          120          125
Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg
    130          135          140
Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys
    145          150          155          160
Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala
    165          170

```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```

His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn
  1      5      10      15
Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val
    20          25          30
Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala
    35          40          45
Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val
    50          55          60
Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala
    65          70          75          80
Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala
    85          90          95
Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg
    100          105          110
Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu
    115          120          125
Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu
    130          135          140
Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
    145          150          155          160
Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu
    165          170

```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```

Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe
  1      5      10      15
Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp
    20          25          30
Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
    35          40          45
Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
    50          55          60
Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu

```

65					70					75				80
Gly	Ala	Gln	Lys	Glu	Ala	Ile	Ser	Pro	Pro	Asp	Ala	Ala	Ser	Ala
				85					90					95
Pro	Leu	Arg	Thr	Ile	Thr	Ala	Asp	Thr	Phe	Arg	Lys	Leu	Phe	Arg
			100					105					110	
Tyr	Ser	Asn	Phe	Leu	Arg	Gly	Lys	Leu	Lys	Leu	Tyr	Thr	Gly	Glu
		115				120					125			Ala
Cys	Arg	Thr	Gly	Asp	Arg	Gly	Gly	Gly	Ser	Ala	Pro	Pro	Arg	Leu
		130				135					140			Ile
Cys	Asp	Ser	Arg	Val	Leu	Glu	Arg	Tyr	Leu	Leu	Glu	Ala	Lys	Glu
145					150					155				Ala
Glu	Asn	Ile	Thr	Thr	Gly	Cys	Ala	Glu	His					160
					165				170					

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Ser	Leu	Asn	Glu	Asn	Ile	Thr	Val	Pro	Asp	Thr	Lys	Val	Asn	Phe	Tyr
1				5					10					15	
Ala	Trp	Lys	Arg	Met	Glu	Val	Gly	Gln	Gln	Ala	Val	Glu	Val	Trp	Gln
			20					25					30		
Gly	Leu	Ala	Leu	Leu	Ser	Glu	Ala	Val	Leu	Arg	Gly	Gln	Ala	Leu	Leu
		35				40						45			
Val	Asn	Ser	Ser	Gln	Pro	Trp	Glu	Pro	Leu	Gln	Leu	His	Val	Asp	Lys
		50				55					60				
Ala	Val	Ser	Gly	Leu	Arg	Ser	Leu	Thr	Thr	Leu	Leu	Arg	Ala	Leu	Gly
65					70					75					80
Ala	Gln	Lys	Glu	Ala	Ile	Ser	Pro	Pro	Asp	Ala	Ala	Ser	Ala	Ala	Pro
				85					90					95	
Leu	Arg	Thr	Ile	Thr	Ala	Asp	Thr	Phe	Arg	Lys	Leu	Phe	Arg	Val	Tyr
		100						105					110		
Ser	Asn	Phe	Leu	Arg	Gly	Lys	Leu	Lys	Leu	Tyr	Thr	Gly	Glu	Ala	Cys
		115				120						125			
Arg	Thr	Gly	Asp	Arg	Gly	Gly	Gly	Ser	Ala	Pro	Pro	Arg	Leu	Ile	Cys
		130				135					140				
Asp	Ser	Arg	Val	Leu	Glu	Arg	Tyr	Leu	Leu	Glu	Ala	Lys	Glu	Ala	Glu
145					150					155					160
Asn	Ile	Thr	Thr	Gly	Cys	Ala	Glu	His	Cys						
				165					170						

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Leu	Asn	Glu	Asn	Ile	Thr	Val	Pro	Asp	Thr	Lys	Val	Asn	Phe	Tyr	Ala
1				5					10					15	
Trp	Lys	Arg	Met	Glu	Val	Gly	Gln	Gln	Ala	Val	Glu	Val	Trp	Gln	Gly
			20					25					30		
Leu	Ala	Leu	Leu	Ser	Glu	Ala	Val	Leu	Arg	Gly	Gln	Ala	Leu	Leu	Val
		35				40						45			
Asn	Ser	Ser	Gln	Pro	Trp	Glu	Pro	Leu	Gln	Leu	His	Val	Asp	Lys	Ala
		50				55					60				
Val	Ser	Gly	Leu	Arg	Ser	Leu	Thr	Thr	Leu	Leu	Arg	Ala	Leu	Gly	Ala
65					70					75					80
Gln	Lys	Glu	Ala	Ile	Ser	Pro	Pro	Asp	Ala	Ala	Ser	Ala	Ala	Pro	Leu
				85					90					95	
Arg	Thr	Ile	Thr	Ala	Asp	Thr	Phe	Arg	Lys	Leu	Phe	Arg	Val	Tyr	Ser
		100						105					110		
Asn	Phe	Leu	Arg	Gly	Lys	Leu	Lys	Leu	Tyr	Thr	Gly	Glu	Ala	Cys	Arg
		115				120						125			

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Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp
 130 135 140
 Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
 145 150 155 160
 Ile Thr Thr Gly Cys Ala Glu His Cys Ser
 165 170

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp
 1 5 10 15
 Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu
 20 25 30
 Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Val Asn
 35 40 45
 Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val
 50 55 60
 Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln
 65 70 75 80
 Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg
 85 90 95
 Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn
 100 105 110
 Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr
 115 120 125
 Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser
 130 135 140
 Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile
 145 150 155 160
 Thr Thr Gly Cys Ala Glu His Cys Ser Leu
 165 170

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys
 1 5 10 15
 Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala
 20 25 30
 Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser
 35 40 45
 Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser
 50 55 60
 Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys
 65 70 75 80
 Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr
 85 90 95
 Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe
 100 105 110
 Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly
 115 120 125
 Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg
 130 135 140
 Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr
 145 150 155 160
 Thr Gly Cys Ala Glu His Cys Ser Leu Asn
 165 170

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(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
 1           5           10           15
Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
          20          25          30
Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
          35          40          45
Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
 50          55          60
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
 65          70          75          80
Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
          85          90          95
Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
          100         105         110
Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp
          115         120         125
Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val
          130         135         140
Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr
145          150          155          160
Gly Cys Ala Glu His Cys Ser Leu Asn Glu
          165          170

```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```

Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
 1           5           10           15
Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu
          20          25          30
Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln
          35          40          45
Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu
 50          55          60
Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala
 65          70          75          80
Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr
          85          90          95
Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg
          100         105         110
Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg
          115         120         125
Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu
          130         135         140
Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly
145          150          155          160
Cys Ala Glu His Cys Ser Leu Asn Glu Asn
          165          170

```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

53

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```

Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
 1      5      10      15
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
 20      25      30
Ala Val Leu Arg Gly Gln Ala Leu Val Asn Ser Ser Gln Pro Trp
 35      40      45
Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
 50      55      60
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
 65      70      75      80
Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp
 85      90      95
Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys
100      105      110
Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly
115      120      125
Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg
130      135      140
Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala
145      150      155      160
Glu His Cys Ser Leu Asn Glu Asn Ile Thr
165      170

```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```

Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly
 1      5      10      15
Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala
 20      25      30
Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu
 35      40      45
Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu
 50      55      60
Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro
 65      70      75      80
Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr
 85      90      95
Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu
100      105      110
Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly
115      120      125
Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr
130      135      140
Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu
145      150      155      160
His Cys Ser Leu Asn Glu Asn Ile Thr Val
165      170

```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```

Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln
 1      5      10      15

```

54

```

Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val
      20      25      30
Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro
      35      40      45
Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr
      50      55      60
Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro
      65      70      75      80
Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe
      85      90      95
Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys
      100      105      110
Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Ser
      115      120      125
Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
      130      135      140
Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His
      145      150      155      160
Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
      165      170

```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```

Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala
  1      5      10      15
Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser
      20      25      30
Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser
      35      40      45
Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys
      50      55      60
Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr
      65      70      75      80
Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe
      85      90      95
Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly
      100      105      110
Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg
      115      120      125
Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr
      130      135      140
Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
      145      150      155      160
Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys
      165      170

```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```

Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
  1      5      10      15
Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
      20      25      30
Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
      35      40      45
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
      50      55      60
Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile

```

65						70				75						80
Thr	Ala	Asp	Thr	Phe	Arg	Lys	Leu	Phe	Arg	Val	Tyr	Ser	Asn	Phe	Leu	
				85					90					95		
Arg	Gly	Lys	Leu	Lys	Leu	Tyr	Thr	Gly	Glu	Ala	Cys	Arg	Thr	Gly	Asp	
			100					105					110			
Arg	Gly	Gly	Gly	Ser	Ala	Pro	Pro	Arg	Leu	Ile	Cys	Asp	Ser	Arg	Val	
		115					120				125					
Leu	Glu	Arg	Tyr	Leu	Leu	Glu	Ala	Lys	Glu	Ala	Glu	Asn	Ile	Thr	Thr	
	130				135						140					
Gly	Cys	Ala	Glu	His	Cys	Ser	Leu	Asn	Glu	Asn	Ile	Thr	Val	Pro	Asp	
145				150						155					160	
Thr	Lys	Val	Asn	Phe	Tyr	Ala	Trp	Lys	Arg							
				165					170							

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Glu 1	Val	Gly	Gln 5	Gln	Ala	Val	Glu	Val	Trp 10	Gln	Gly	Leu	Ala	Leu 15	Leu
Ser	Glu	Ala	Val 20	Leu	Arg	Gly	Gln	Ala 25	Leu	Leu	Val	Asn 30	Ser	Ser	Gln
Pro	Trp	Glu 35	Pro	Leu	Gln	Leu	His 40	Val	Asp	Lys	Ala	Val 45	Ser	Gly	Leu
Arg	Ser 50	Leu	Thr	Thr	Leu	Leu 55	Arg	Ala	Leu	Gly	Ala 60	Gln	Lys	Glu	Ala
Ile 65	Ser	Pro	Pro	Asp 70	Ala	Ala	Ser	Ala	Ala	Pro 75	Leu	Arg	Thr	Ile	Thr 80
Ala	Asp	Thr	Phe 85	Arg	Lys	Leu	Phe	Arg	Val 90	Tyr	Ser	Asn	Phe 95	Leu	Arg
Gly	Lys	Leu	Lys 100	Leu	Tyr	Thr	Gly	Glu 105	Ala	Cys	Arg	Thr	Gly 110	Asp	Arg
Gly	Gly 115	Gly	Ser	Ala	Pro	Pro	Arg 120	Leu	Ile	Cys	Asp	Ser 125	Arg	Val	Leu
Glu	Arg 130	Tyr	Leu	Leu	Glu	Ala 135	Lys	Glu	Ala	Glu	Asn 140	Ile	Thr	Thr	Gly
Cys 145	Ala	Glu	His	Cys	Ser 150	Leu	Asn	Glu	Asn	Ile 155	Thr	Val	Pro	Asp	Thr 160
Lys	Val	Asn	Phe 165	Tyr	Ala	Trp	Lys	Arg	Met 170						

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Val	Gly	Gln	Gln	Ala	Val	Glu	Val	Trp	Gln	Gly	Leu	Ala	Leu	Leu	Ser
1				5					10					15	
Glu	Ala	Val	Leu	Arg	Gly	Gln	Ala	Leu	Leu	Val	Asn	Ser	Ser	Gln	Pro
			20					25					30		
Trp	Glu	Pro	Leu	Gln	Leu	His	Val	Asp	Lys	Ala	Val	Ser	Gly	Leu	Arg
		35					40					45			
Ser	Leu	Thr	Thr	Leu	Leu	Arg	Ala	Leu	Gly	Ala	Gln	Lys	Glu	Ala	Ile
	50					55					60				
Ser	Pro	Pro	Asp	Ala	Ala	Ser	Ala	Ala	Pro	Leu	Arg	Thr	Ile	Thr	Ala
65					70					75					80
Asp	Thr	Phe	Arg	Lys	Leu	Phe	Arg	Val	Tyr	Ser	Asn	Phe	Leu	Arg	Gly
				85					90					95	
Lys	Leu	Lys	Leu	Tyr	Thr	Gly	Glu	Ala	Cys	Arg	Thr	Gly	Asp	Arg	Gly
			100					105					110		
Gly	Gly	Ser	Ala	Pro	Pro	Arg	Leu	Ile	Cys	Asp	Ser	Arg	Val	Leu	Glu
		115					120					125			

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Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys
 130 135 140
 Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys
 145 150 155 160
 Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
 165 170

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu
 1 5 10 15
 His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu
 20 25 30
 Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala
 35 40 45
 Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu
 50 55 60
 Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr
 65 70 75 80
 Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro
 85 90 95
 Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala
 100 105 110
 Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu
 115 120 125
 Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp
 130 135 140
 Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu
 145 150 155 160
 Ala Leu Leu Ser Glu Ala Val Leu Arg Gly
 165 170

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His
 1 5 10 15
 Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg
 20 25 30
 Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser
 35 40 45
 Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe
 50 55 60
 Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly
 65 70 75 80
 Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg
 85 90 95
 Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys
 100 105 110
 Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn
 115 120 125
 Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys
 130 135 140
 Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala
 145 150 155 160
 Leu Leu Ser Glu Ala Val Leu Arg Gly Gln
 165 170

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(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```

Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val
 1      5      10      15
Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala
 20      25      30
Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala
 35      40      45
Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg
 50      55      60
Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu
 65      70      75      80
Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu
 85      90      95
Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
100      105      110
Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu
115      120      125
Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
130      135      140
Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
145      150      155      160
Leu Ser Glu Ala Val Leu Arg Gly Gln Ala
165      170

```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```

Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
 1      5      10      15
Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
 20      25      30
Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
 35      40      45
Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
 50      55      60
Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
 65      70      75      80
Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile
 85      90      95
Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala
100      105      110
Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn
115      120      125
Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
130      135      140
Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu
145      150      155      160
Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
165      170

```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

58

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```

Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys
1      5      10      15
Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly
20      25      30
Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro
35      40      45
Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr
50      55      60
Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys
65      70      75      80
Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys
85      90      95
Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu
100      105      110
Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile
115      120      125
Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
130      135      140
Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
145      150      155      160
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu
165      170

```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```

Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala
1      5      10      15
Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala
20      25      30
Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu
35      40      45
Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser
50      55      60
Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg
65      70      75      80
Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp
85      90      95
Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
100      105      110
Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr
115      120      125
Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
130      135      140
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
145      150      155      160
Ala Val Leu Arg Gly Gln Ala Leu Leu Val
165      170

```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```

Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val
1      5      10      15

```

59

```

Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln
      20      25      30
Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg
      35      40      45
Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn
      50      55      60
Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr
      65      70      75      80
Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser
      85      90      95
Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile
      100      105      110
Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val
      115      120      125
Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly
      130      135      140
Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala
      145      150      155      160
Val Leu Arg Gly Gln Ala Leu Leu Val Asn
      165      170

```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```

Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser
  1      5      10      15
Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys
      20      25      30
Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr
      35      40      45
Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe
      50      55      60
Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly
      65      70      75      80
Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg
      85      90      95
Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr
      100      105      110
Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro
      115      120      125
Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln
      130      135      140
Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val
      145      150      155      160
Leu Arg Gly Gln Ala Leu Leu Val Asn Ser
      165      170

```

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```

Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
  1      5      10      15
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
      20      25      30
Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
      35      40      45
Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
      50      55      60
Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp

```

60

65	70	75	80
Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val			
	85	90	95
Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr			
	100	105	110
Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp			
	115	120	125
Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln			
	130	135	140
Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu			
	145	150	155
Arg Gly Gln Ala Leu Leu Val Asn Ser Ser			160
	165	170	

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu	
1 5 10 15	
Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala	
20 25 30	
Ile Ser Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr	
35 40 45	
Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg	
50 55 60	
Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg	
65 70 75 80	
Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu	
85 90 95	
Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly	
100 105 110	
Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr	
115 120 125	
Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala	
130 135 140	
Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg	
145 150 155 160	
Gly Gln Ala Leu Leu Val Asn Ser Ser Gln	
165 170	

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg	
1 5 10 15	
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile	
20 25 30	
Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala	
35 40 45	
Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly	
50 55 60	
Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly	
65 70 75 80	
Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu	
85 90 95	
Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys	
100 105 110	
Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys	
115 120 125	

61

```

Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val
 130      135      140
Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly
145      150      155      160
Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
      165      170

```

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```

Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
 1      5      10      15
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
 20      25      30
Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp
 35      40      45
Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys
 50      55      60
Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly
 65      70      75      80
Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg
 85      90      95
Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala
100      105      110
Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val
115      120      125
Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu
130      135      140
Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln
145      150      155      160
Ala Leu Leu Val Asn Ser Ser Gln Pro Trp
      165      170

```

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

```

Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala
 1      5      10      15
Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys
 20      25      30
Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr
 35      40      45
Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Ser Ala Pro
 50      55      60
Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu
 65      70      75      80
Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser
 85      90      95
Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala
100      105      110
Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly
115      120      125
Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val
130      135      140
Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala
145      150      155      160
Val Ser Gly Leu Arg Ser Leu Thr Thr Leu
      165      170

```

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```

Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala
 1           5           10          15
Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu
 20          25          30
Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr
 35          40          45
Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Ser Ala Pro Pro
 50          55          60
Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala
 65          70          75          80
Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu
 85          90          95
Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp
100         105         110
Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu
115         120         125
Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn
130         135         140
Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val
145         150         155         160
Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu
165         170

```

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

```

Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser
 1           5           10          15
Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe
 20          25          30
Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly
 35          40          45
Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg
 50          55          60
Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys
 65          70          75          80
Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn
 85          90          95
Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys
100         105         110
Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala
115         120         125
Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser
130         135         140
Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser
145         150         155         160
Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg
165         170

```

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

63

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

```

Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala
 1      5      10      15
Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg
 20      25      30
Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu
 35      40      45
Ala Cys Arg Thr Gly Asp Arg Gly Gly Ser Ala Pro Pro Arg Leu
 50      55      60
Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
 65      70      75      80
Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu
 85      90      95
Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
100      105      110
Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
115      120      125
Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
130      135      140
Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
145      150      155      160
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala
165      170

```

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

```

Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
 1      5      10      15
Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val
 20      25      30
Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala
 35      40      45
Cys Arg Thr Gly Asp Arg Gly Gly Ser Ala Pro Pro Arg Leu Ile
 50      55      60
Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala
 65      70      75      80
Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn
 85      90      95
Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met
100      105      110
Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu
115      120      125
Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln
130      135      140
Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu
145      150      155      160
Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
165      170

```

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

```

Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro
 1      5      10      15

```

64

```

Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr
20 25 30
Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys
35 40 45
Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys
50 55 60
Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu
65 70 75 80
Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile
85 90 95
Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
100 105 110
Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
115 120 125
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
130 135 140
Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
145 150 155 160
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly
165 170

```

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

```

Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu
1 5 10 15
Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser
20 25 30
Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg
35 40 45
Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp
50 55 60
Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
65 70 75 80
Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr
85 90 95
Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
100 105 110
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
115 120 125
Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp
130 135 140
Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
145 150 155 160
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala
165 170

```

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

```

Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg
1 5 10 15
Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn
20 25 30
Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr
35 40 45
Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser
50 55 60
Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile

```

65

65	70	75	80
Thr Thr Gly Cys Ala Glu His Cys Ser	Leu Asn Glu Asn Ile Thr Val		
	85	90	95
Pro Asp Thr Lys Val Asn Phe Tyr Ala	Trp Lys Arg Met Glu Val Gly		
	100	105	110
Gln Gln Ala Val Glu Val Trp Gln Gly	Leu Ala Leu Leu Ser Glu Ala		
	115	120	125
Val Leu Arg Gly Gln Ala Leu Leu Val	Asn Ser Ser Gln Pro Trp Glu		
	130	135	140
Pro Leu Gln Leu His Val Asp Lys Ala	Val Ser Gly Leu Arg Ser Leu		
	145	150	155
Thr Thr Leu Leu Arg Ala Leu Gly Ala	Gln		
	165	170	

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Glu Ala Ile Ser Pro Pro Asp Ala Ala Ser	Ala Ala Pro Leu Arg Thr
1	5 10 15
Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe	Arg Val Tyr Ser Asn Phe
	20 25 30
Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly	Glu Ala Cys Arg Thr Gly
	35 40 45
Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg	Leu Ile Cys Asp Ser Arg
	50 55 60
Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys	Glu Ala Glu Asn Ile Thr
	65 70 75 80
Thr Gly Cys Ala Glu His Cys Ser Leu Asn	Glu Asn Ile Thr Val Pro
	85 90 95
Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys	Arg Met Glu Val Gly Gln
	100 105 110
Gln Ala Val Glu Val Trp Gln Gly Leu Ala	Leu Leu Ser Glu Ala Val
	115 120 125
Leu Arg Gly Gln Ala Leu Leu Val Asn Ser	Ser Gln Pro Trp Glu Pro
	130 135 140
Leu Gln Leu His Val Asp Lys Ala Val Ser	Gly Leu Arg Ser Leu Thr
	145 150 155 160
Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys	
	165 170

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Ala Ile Ser Pro Pro Asp Ala Ala Ser	Ala Ala Pro Leu Arg Thr Ile
1	5 10 15
Thr Ala Asp Thr Phe Arg Lys Leu Phe	Arg Val Tyr Ser Asn Phe Leu
	20 25 30
Arg Gly Lys Leu Lys Leu Tyr Thr Gly	Glu Ala Cys Arg Thr Gly Asp
	35 40 45
Arg Gly Gly Gly Ser Ala Pro Arg Leu Ile	Cys Asp Ser Arg Val
	50 55 60
Leu Glu Arg Tyr Leu Leu Glu Ala Lys	Glu Ala Glu Asn Ile Thr Thr
	65 70 75 80
Gly Cys Ala Glu His Cys Ser Leu Asn	Glu Asn Ile Thr Val Pro Asp
	85 90 95
Thr Lys Val Asn Phe Tyr Ala Trp Lys	Arg Met Glu Val Gly Gln Gln
	100 105 110
Ala Val Glu Val Trp Gln Gly Leu Ala	Leu Leu Ser Glu Ala Val Leu
	115 120 125

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```

Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu
 130          135          140
Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr
145          150          155          160
Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
          165          170

```

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```

Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr
 1          5          10          15
Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg
          20          25          30
Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg
          35          40          45
Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu
50          55          60
Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly
65          70          75          80
Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr
          85          90          95
Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala
          100          105          110
Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg
          115          120          125
Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln
130          135          140
Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu
145          150          155          160
Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala
          165          170

```

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

```

Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala
 1          5          10          15
Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly
          20          25          30
Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly
          35          40          45
Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu
50          55          60
Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys
65          70          75          80
Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys
          85          90          95
Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Ala Val
          100          105          110
Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly
          115          120          125
Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu
130          135          140
His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu
145          150          155          160
Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile
          165          170

```

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(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

```

Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp
 1          5          10          15
Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys
 20          25          30
Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly
 35          40          45
Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg
 50          55          60
Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala
 65          70          75          80
Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val
 85          90          95
Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu
100          105          110
Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln
115          120          125
Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His
130          135          140
Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg
145          150          155          160
Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
165          170

```

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```

Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr
 1          5          10          15
Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu
 20          25          30
Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly
 35          40          45
Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr
 50          55          60
Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu
 65          70          75          80
His Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn
 85          90          95
Phe Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val
100          105          110
Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala
115          120          125
Leu Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val
130          135          140
Asp Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala
145          150          155          160
Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro
165          170

```

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

```

Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe
 1      5      10      15
Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys
 20      25      30
Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser
 35      40      45
Ala Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu
 50      55      60
Leu Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His
 65      70      75      80
Cys Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe
 85      90      95
Tyr Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp
 100      105      110
Gln Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu
 115      120      125
Leu Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp
 130      135      140
Lys Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu
 145      150      155      160
Gly Ala Gln Lys Glu Ala Ile Ser Pro Pro
 165      170

```

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

```

Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg
 1      5      10      15
Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu
 20      25      30
Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala
 35      40      45
Pro Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu
 50      55      60
Glu Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys
 65      70      75      80
Ser Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr
 85      90      95
Ala Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln
 100      105      110
Gly Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu
 115      120      125
Val Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys
 130      135      140
Ala Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly
 145      150      155      160
Ala Gln Lys Glu Ala Ile Ser Pro Pro Asp
 165      170

```

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

```

Ala Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys
 1      5      10      15

```

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```

Leu Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr
    20      25      30
Thr Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro
    35      40      45
Pro Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu
    50      55      60
Ala Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser
    65      70      75      80
Leu Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala
    85      90      95
Trp Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly
    100     105     110
Leu Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val
    115     120     125
Asn Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala
    130     135     140
Val Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala
    145     150     155     160
Gln Lys Glu Ala Ile Ser Pro Pro Asp Ala
    165     170

```

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

```

Ser Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu
  1      5      10      15
Phe Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr
    20      25      30
Gly Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro
    35      40      45
Arg Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala
    50      55      60
Lys Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu
    65      70      75      80
Asn Glu Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp
    85      90      95
Lys Arg Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu
    100     105     110
Ala Leu Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Val Asn
    115     120     125
Ser Ser Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val
    130     135     140
Ser Gly Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln
    145     150     155     160
Lys Glu Ala Ile Ser Pro Pro Asp Ala Ala
    165     170

```

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

```

Ala Ala Pro Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe
  1      5      10      15
Arg Val Tyr Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly
    20      25      30
Glu Ala Cys Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg
    35      40      45
Leu Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys
    50      55      60
Glu Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn

```

65					70				75				80
Glu	Asn	Ile	Thr	Val	Pro	Asp	Thr	Lys	Val	Asn	Phe	Tyr	Ala
				85					90				95
Arg	Met	Glu	Val	Gly	Gln	Gln	Ala	Val	Glu	Val	Trp	Gln	Gly
			100					105					110
Leu	Leu	Ser	Glu	Ala	Val	Leu	Arg	Gly	Gln	Ala	Leu	Leu	Val
		115					120					125	Asn
Ser	Gln	Pro	Trp	Glu	Pro	Leu	Gln	Leu	His	Val	Asp	Lys	Ala
		130					135					140	Val
Gly	Leu	Arg	Ser	Leu	Thr	Thr	Leu	Leu	Arg	Ala	Leu	Gly	Ala
					150					155			Gln
145													Lys
Glu	Ala	Ile	Ser	Pro	Pro	Asp	Ala	Ala	Ser				160
					165				170				

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Ala	Pro	Leu	Arg	Thr	Ile	Thr	Ala	Asp	Thr	Phe	Arg	Lys	Leu	Phe	Arg
1				5					10					15	
Val	Tyr	Ser	Asn	Phe	Leu	Arg	Gly	Lys	Leu	Lys	Leu	Tyr	Thr	Gly	Glu
			20					25					30		
Ala	Cys	Arg	Thr	Gly	Asp	Arg	Gly	Gly	Gly	Ser	Ala	Pro	Pro	Arg	Leu
		35					40					45			
Ile	Cys	Asp	Ser	Arg	Val	Leu	Glu	Arg	Tyr	Leu	Leu	Glu	Ala	Lys	Glu
	50					55					60				
Ala	Glu	Asn	Ile	Thr	Thr	Gly	Cys	Ala	Glu	His	Cys	Ser	Leu	Asn	Glu
					70					75				80	
Asn	Ile	Thr	Val	Pro	Asp	Thr	Lys	Val	Asn	Phe	Tyr	Ala	Trp	Lys	Arg
			85						90					95	
Met	Glu	Val	Gly	Gln	Gln	Ala	Val	Glu	Val	Trp	Gln	Gly	Leu	Ala	Leu
			100					105					110		
Leu	Ser	Glu	Ala	Val	Leu	Arg	Gly	Gln	Ala	Leu	Leu	Val	Asn	Ser	Ser
		115					120					125			
Gln	Pro	Trp	Glu	Pro	Leu	Gln	Leu	His	Val	Asp	Lys	Ala	Val	Ser	Gly
		130					135				140				
Leu	Arg	Ser	Leu	Thr	Thr	Leu	Leu	Arg	Ala	Leu	Gly	Ala	Gln	Lys	Glu
					150					155				160	
Ala	Ile	Ser	Pro	Pro	Asp	Ala	Ala	Ser	Ala						
				165					170						

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Pro	Leu	Arg	Thr	Ile	Thr	Ala	Asp	Thr	Phe	Arg	Lys	Leu	Phe	Arg	Val
1				5					10					15	
Tyr	Ser	Asn	Phe	Leu	Arg	Gly	Lys	Leu	Lys	Leu	Tyr	Thr	Gly	Glu	Ala
		20					25						30		
Cys	Arg	Thr	Gly	Asp	Arg	Gly	Gly	Gly	Ser	Ala	Pro	Pro	Arg	Leu	Ile
		35				40					45				
Cys	Asp	Ser	Arg	Val	Leu	Glu	Arg	Tyr	Leu	Leu	Glu	Ala	Lys	Glu	Ala
	50					55					60				
Glu	Asn	Ile	Thr	Thr	Gly	Cys	Ala	Glu	His	Cys	Ser	Leu	Asn	Glu	Asn
				70					75					80	
Ile	Thr	Val	Pro	Asp	Thr	Lys	Val	Asn	Phe	Tyr	Ala	Trp	Lys	Arg	Met
			85						90					95	
Glu	Val	Gly	Gln	Gln	Ala	Val	Glu	Val	Trp	Gln	Gly	Leu	Ala	Leu	Leu
		100					105					110			
Ser	Glu	Ala	Val	Leu	Arg	Gly	Gln	Ala	Leu	Leu	Val	Asn	Ser	Ser	Gln
		115				120					125				

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```

Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu
130                               135          140
Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala
145                               150          155          160
Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala
                               165          170

```

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 171 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

```

Leu Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr
1      5      10      15
Ser Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys
20      25      30
Arg Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys
35      40      45
Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu
50      55      60
Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile
65      70      75      80
Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu
85      90      95
Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser
100     105     110
Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro
115     120     125
Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg
130     135     140
Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Ala Lys Glu Ala
145     150     155     160
Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro
165     170

```

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

```

Arg Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser
1      5      10      15
Asn Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg
20      25      30
Thr Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp
35      40      45
Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn
50      55      60
Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr
65      70      75      80
Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val
85      90      95
Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu
100     105     110
Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp
115     120     125
Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser
130     135     140
Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser
145     150     155     160
Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu
165     170

```

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(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

```

Thr Ile Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn
 1           5           10           15
Phe Leu Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr
          20           25           30
Gly Asp Arg Gly Gly Gly Ser Ala Pro Pro Arg Leu Ile Cys Asp Ser
          35           40           45
Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu Ala Glu Asn Ile
          50           55           60
Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu Asn Ile Thr Val
          65           70           75           80
Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg Met Glu Val Gly
          85           90           95
Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu Leu Ser Glu Ala
          100          105          110
Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser Gln Pro Trp Glu
          115          120          125
Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly Leu Arg Ser Leu
          130          135          140
Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu Ala Ile Ser Pro
          145          150          155          160
Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg
          165          170

```

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

```

AATATCACGA CGGGCTGTGC TGAACACTGC AGCTTGAATG AGAATATCAC TGTCCCAGAC      60
ACCAAGTTA ATTTCTATGC CTGGAAGAGG ATGGAGGTCG GGCAGCAGGC CGTAGAAGTC      120
TGGCAGGGCC TGGCCCTGCT GTCGGAAGCT GTCCTGCGGG GCCAGGCCCT GTTGGTCAAC      180
TCTTCCCAGC CGTGGGAGCC CCTGCAGCTG CATGTGGATA AAGCCGTCAG TGGCCTTCGC      240
AGCCTCACCA CTCTGCTTCG GGCTCTGGGA GCCCAGAAGG AAGCCATCTC CCTCCAGAT      300
GCGGCCTCAG CTGCTCCACT CCGAACAATC ACTGCTGACA CTTTCCGCAA ACTCTCCGA      360
GTCTACTCCA ATTTCTCTCG GGGAAAGCTG AAGCTGTACA CAGGGGAGGC CTGCAGGACA      420
GGGGACAGAT GAGGCGGCGG CTCCCCCAC CACGCCCTCAT CTGTGACAGC CGAGTCTTGG      480
AGAGGTACCT CTTGGAGGCC AAGGAGGCCG AG                                     512

```

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

```

ATCACGACGG GCTGTGCTGA ACACTGCAGC TTGAATGAGA ATATCACTGT CCCAGACACC      60
AAAGTTAATT TCTATGCCCTG GAAGAGGATG GAGGTCGGGC AGCAGGCCCGT AGAAGTCTGG      120
CAGGGCCTGG CCCTGCTGTC GGAAGCTGTC CTGCGGGGCC AGGCCCTGTT GGTCAACTCT      180
TCCCAGCCGT GGGAGCCCTT GCAGCTGCAT GTGGATAAAG CCGTCAGTGG CCTTCGCAGC      240
CTCACCACTC TGCTTCGGGC TCTGGGAGCC CAGAAGGAAG CCATCTCCCC TCCAGATGCG      300
GCCTCAGCTG CTCCACTCCG AACAACTACT GCTGACACTT TCCGCAAACCT CTTCGGAGTC      360
TACTCCAATT TCCTCCGGGG AAAGCTGAAG CTGTACACAG GGGAGGCCCTG CAGGACAGGG      420
GACAGATGAG GCGGCGGCTC CCCCCACCAC GCCTCATCTG TGACAGCCGA GTCCTGGAGA      480
GGTACCTCTT GGAGGCCAAG GAGGCCGAGA AT                                     512

```

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(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

```

ACGACGGGCT GTGCTGAACA CTGCAGCTTG AATGAGAATA TCACTGTCCC AGACACCAAA    60
GTTAATTTCT ATGCCTGGAA GAGGATGGAG GTCGGGCAGC AGGCCGTAGA AGTCTGGCAG    120
GGCCTGGCCC TGCTGTCCGA AGCTGTCTCT CGGGGCCAGG CCCTGTTGGT CAACTCTTCC    180
CAGCCCTGGG AGCCCTGCA GCTGCATGTG GATAAAGCCG TCAGTGGCCT TCGCAGCCTC    240
ACCACTCTGC TTCGGGCTCT GGGAGCCAG AAGGAAGCCA TCTCCCTCC AGATGCGGCC    300
TCAGCTGCTC CACTCCGAAC AATCACTGCT GACACTTTCC GCAAACCTTT CCGAGTCTAC    360
TCCAATTTCC TCCGGGAAA GCTGAAGCTG TACACAGGG AGGCCTGCAG GACAGGGGAC    420
AGATGAGGCG GCGGCTCCC CCACCAGCC TCATCTGTGA CAGCCGAGTC CTGGAGAGGT    480
ACCTCTTGGA GGCAAGGAG GCCGAGAATA TC                                     512

```

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

```

ACGGGCTGTG CTGAACACTG CAGCTTGAAT GAGAATATCA CTGTCCCAGA CACCAAAGTT    60
AATTTCTATG CCTGGAAGAG GATGGAGGTC GGGCAGCAGG CCGTAGAAGT CTGGCAGGGC    120
CTGGCCCTGC TGTCGGAAGC TGTCCTGCGG GGCCAGGCC TGTGGTCAA CTCTTCCCAG    180
CCGTGGGAGC CCTGCGAGCT GCATGTGGAT AAAGCCGTCA GTGGCCTTCG CAGCCTCACC    240
ACTCTGTCTC GGGCTCTGGG AGCCCAGAAG GAAGCCATCT CCCCTCCAGA TGGCGCCTCA    300
GCTGCTCCAC TCCGAACAAT CACTGCTGAC ACTTTCCGCA AACTCTTCCG AGTCTACTCC    360
AATTTCTCTC GGGGAAAGCT GAAGCTGTAC ACAGGGGAGG CCTGCAGGAC AGGGGACAGA    420
TGAGGGCGCG GCTCCCCCA CCACGCCTCA TCTGTGACAG CCGAGTCTTG GAGAGGTACC    480
TCTTGAGGCG CAAGGAGGCC GAGAATATCA CG                                     512

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(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

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GGCTGTGCTG AACACTGCAG CTTGAATGAG AATATCACTG TCCCAGACAC CAAAGTTAAT    60
TTCTATGCCT GGAAGAGGAT GGAGGTCGGG CAGCAGGCCG TAGAAGTCTG GCAGGGCCTG    120
GCCCTGCTGT CGGAAGCTGT CCTGCGGGG CAGGCCCTGT TGGTCAACTC TTCCCAGCCG    180
TGGGAGCCCC TGCAGCTGCA TGTGGATAAA GCCGTCAGTG GCCTTCGCAG CCTCACCCT    240
CTGCTTCGGG CTCTGGGAGC CCAGAAGGAA GCCATCTCCC CTCCAGATGC GGCCTCAGCT    300
GCTCCACTCC GAACAATCAC TGCTGACACT TTCCGCAAAC TCTTCCGAGT CTACTCCAAT    360
TTCTTCCGGG GAAAGCTGAA GCTGTACACA GGGGAGGCCT GCAGGACAGG GGACAGATGA    420
GGCGGCGGCT CCCCCACCA CGCCTCATCT GTGACAGCCG AGTCCTGGAG AGGTACCTCT    480
TGGAGGCCAA GGAGGCCGAG AATATCACGA CG                                     512

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(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

```

TGTGCTGAAC ACTGCAGCTT GAATGAGAAT ATCACTGTCC CAGACACCAA AGTTAATTTT    60
TATGCCTGGA AGAGGATGGA GGTGGGCGC CAGGCCGTAG AAGTCTGGCA GGGCCTGGCC    120
CTGCTGTCCG AAGTGTCTCT CGGGGCCAG GCCCTGTTGG TCAACTCTTC CCAGCCGTGG    180

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GAGCCCCTGC	AGCTGCATGT	GGATAAAGCC	GTCAGTGGCC	TTCGCAGCCT	CACCACTCTG	240
CTTCGGGCTC	TGGGAGCCCA	GAAGGAAGCC	ATCTCCCCCTC	CAGATGCGGC	CTCAGCTGCT	300
CCACTCCGAA	CAATCACTGC	TGACACTTTC	CGCAAACCTCT	TCCGAGTCTA	CTCCAATTTC	360
CTCCGGGGAA	AGCTGAAGCT	GTACACAGGG	GAGGCCTGCA	GGACAGGGGA	CAGATGAGGC	420
GGCGGCTCCC	CCCACCACGC	CTCATCTGTG	ACAGCCGAGT	CCTGGAGAGG	TACCTCTTGG	480
AGGCCAAGGA	GGCCGAGAAT	ATCACGACGG	GC			512

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GCTGAACACT	GCAGCTTGAA	TGAGAATATC	ACTGTCCCAG	ACACCAAAGT	TAATTTCTAT	60
GCCTGGAAGA	GGATGGAGGT	CGGGCAGCAG	GCCGTAGAAG	TCTGGCAGGG	CCTGGCCCCTG	120
CTGTCCGAAG	CTGTCCCTGCG	GGGCCAGGCC	CTGTTGGTCA	ACTCTTCCCA	GCCGTGGGAG	180
CCCCTGCAGC	TGCATGTGGA	TAAAGCCGTC	AGTGGCCTTC	GCAGCCTCAC	CACTCTGCTT	240
CGGGCTCTGG	GAGCCCAGAA	GGAAGCCATC	TCCCCTCCAG	ATGCGGCCTC	AGCTGCTCCA	300
CTCCGAACAA	TCACTGCTGA	CACCTTCCGC	AAACTCTTCC	GAGTCTACTC	CAATTTCTCTC	360
CGGGGAAAGC	TGAAGCTGTA	CACAGGGGAG	GCCTGCAGGA	CAGGGGACAG	ATGAGGCGGC	420
GGCTCCCCCC	ACCACGCCTC	ATCTGTGACA	GCCGAGTCCT	GGAGAGGTAC	CTCTTGAGAG	480
CCAAGGAGGC	CGAGAAATATC	ACGACGGGCT	GT			512

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GAACACTGCA	GCTTGAATGA	GAATATCACT	GTCCAGACA	CCAAAGTTAA	TTTCTATGCC	60
TGGAAGAGGA	TGGAGGTCGG	GCAGCAGGCC	GTAGAAGTCT	GGCAGGGCCT	GGCCCTGCTG	120
TCGGAAGCTG	TCCTGCGGGG	CCAGGCCCTG	TTGGTCAACT	CTTCCAGCC	GTGGGAGCCC	180
CTGCAGCTGC	ATGTGGATAA	AGCCGTCAGT	GGCCTTCGCA	GCCTCACCAC	TCTGCTTCGG	240
GCTCTGGGAG	CCCAGAAGGA	AGCCATCTCC	CCTCCAGATG	CGGCCTCAGC	TGCTCCACTC	300
CGAACAAATCA	CTGCTGACAC	TTTCCGCAAA	CTCTTCCGAG	TCTACTCCAA	TTTCTTCCGG	360
GGAAAGCTGA	AGCTGTACAC	AGGGGAGGCC	TGCAGGACAG	GGGACAGATG	AGGCGGCGGC	420
TCCCCCACC	ACGCCTCATC	TGTGACAGCC	GAGTCCTGGA	GAGGTACTCT	TTGGAGGCCA	480
AGGAGGCCGA	GAATATCACG	ACGGGCTGTG	CT			512

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

CACTGCAGCT	TGAATGAGAA	TATCACTGTC	CCAGACACCA	AAGTTAATTT	CTATGCCTGG	60
AAGAGGATGG	AGGTGCGGCA	GCAGGCCGTA	GAAGTCTGGC	AGGGCCTGGC	CCTGCTGTG	120
GAAGCTGTCC	TGCGGGGCCA	GGCCCTGTTG	GTCAACTCTT	CCCAGCCGTG	GGAGCCCCTG	180
CAGCTGCATG	TGATAAAGC	CGTCAGTGGC	CTTCGCAGCC	TCACCACTCT	GCTTCGGGCT	240
CTGGGAGCCC	AGAAGGAAGC	CATCTCCCCT	CCAGATGCGG	CCTCAGCTGC	TCCACTCCGA	300
ACAATCACTG	CTGACACTTT	CCGCAAATC	TTCCGAGTCT	ACTCCAATTT	CCTCCGGGGA	360
AAGCTGAAGC	TGTACACAGG	GGAGGCCTGC	AGGACAGGGG	ACAGATGAGG	CGGCGGCTCC	420
CCCCACCACG	CCTCATCTGT	GACAGCCGAG	TCCTGGAGAG	GTACCTCTTG	GAGGCCAAGG	480
AGGCCGAGAA	TATCACGACG	GGCTGTGCTG	AA			512

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

TGCAGCTTGA	ATGAGAATAT	CACTGTCCCA	GACACCAAAG	TTAATTTCTA	TGCCTGGAAG	60
AGGATGGAGG	TCGGGCAGCA	GGCCGTAGAA	GTCTGGCAGG	GCCTGGCCCT	GCTGTGGGAA	120
GCTGTCCCTG	GGGGCCAGGC	CCTGTGTGGT	AACTCTTCCC	AGCCGTGGGA	GCCCCTGAG	180
CTGCATGTGG	ATAAAGCCGT	CAGTGGCCTT	CGCAGCCTCA	CCACTCTGCT	TCGGGCTCTG	240
GGAGCCCAGA	AGGAAGCCAT	CTCCCCCTCA	GATGCGGCCT	CAGCTGCTCC	ACTCCGAACA	300
ATCACTGCTG	ACACTTTCCG	CAAACTCTTC	CGAGTCTACT	CCAATTTCTT	CCGGGGAAAG	360
CTGAAGCTGT	ACACAGGGGA	GGCCTGCAGG	ACAGGGGACA	GATGAGGCGG	CGGCTCCCCC	420
CACCACGCCT	CATCTGTGAC	AGCCGAGTCC	TGGAGAGGTA	CCTCTTGGAG	GCCAAGGAGG	480
CCGAGAATAT	CACGACGGGC	TGTGCTGAAC	AC			512

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

AGCTTGAATG	AGAATATCAC	TGTCCAGAC	ACCAAAGTTA	ATTCTATGC	CTGGAAGAGG	60
ATGGAGGTGC	GGCAGCAGGC	CGTAGAAGTC	TGGCAGGGCC	TGGCCCTGCT	GTCCGAAGCT	120
GTCCTGCGGG	GCCAGGCCCT	GTTGGTCAAC	TCTTCCAGC	CGTGGGAGCC	CCTGCAGCTG	180
CATGTGGATA	AAGCCGTACG	TGGCCTTCGC	AGCCTACCA	CTCTGCTTCG	GGCTCTGGGA	240
GCCCAGAAGG	AAGCCATCTC	CCCTCCAGAT	GCGGCCCTCAG	CTGCTCCACT	CCGAACAATC	300
ACTGCTGACA	CTTTCGCAA	ACTCTTCCGA	GTCTACTCCA	ATTCTCTCCG	GGGAAAGCTG	360
AAGCTGTACA	CAGGGGAGGC	CTGCAGGACA	GGGGACAGAT	GAGGCGGCGG	CTCCCCCAC	420
CACGCCCTCAT	CTGTGACAGC	CGAGTCCTGG	AGAGGTACCT	CTTGGAGGCC	AAGGAGGCCG	480
AGAATATCAC	GACGGGCTGT	GCTGAACACT	GC			512

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

TTGAATGAGA	ATATCACTGT	CCCAGACACC	AAAGTTAATT	TCTATGCCTG	GAAGAGGATG	60
GAGGTGCGGC	AGCAGGCCGT	AGAAGTCTGG	CAGGGCCTGG	CCCTGCTGTC	GGAAGCTGTC	120
CTGCGGGGCC	AGGCCCTGTT	GGTCAACTCT	TCCCAGCCGT	GGGAGCCCTT	GCAGCTGCAT	180
GTGGATAAAG	CCGTCACTGG	CCTTCGCAGC	CTCACCCTC	TGCTTCGGGC	TCTGGGAGCC	240
CAGAAGGAAG	CCATCTCCCC	TCCAGATGCG	GCCTCAGCTG	TCCACTCCG	AACAATCACT	300
GCTGACACTT	TCCGCAAACT	CTTCCGAGTC	TACTCCAATT	TCCTCCGGGG	AAAGCTGAAG	360
CTGTACACAG	GGGAGGCCTG	CAGGACAGGG	GACAGATGAG	GCGGCGGCTC	CCCCACCAC	420
GCCTCATCTG	TGACAGCCGA	GTCTGGAGA	GGTACCTCTT	GGAGGCCAAG	GAGGCCGAGA	480
ATATCACGAC	GGGTGTGCT	GAACACTGCA	GC			512

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

AATGAGAATA	TCACTGTCCC	AGACACCAAA	GTAAATTTCT	ATGCCTGGAA	GAGGATGGAG	60
GTCGGGCAGC	AGGCCGTAGA	AGTCTGGCAG	GGCCTGGCCC	TGCTGTGGGA	AGCTGTCCCTG	120
CGGGGCCAGG	CCCTGTTGGT	CAACTCTTCC	CAGCCGTGGG	AGCCCTTGCA	GCTGCATGTG	180
GATAAAGCCG	TCACTGGCCT	TCGCAGCCTC	ACCACTCTGC	TTCCGGGCTCT	GGGAGCCCAG	240
AAGGAAGCCA	TCTCCCTCC	AGATGCGGCC	TCAGCTGCTC	CACTCCGAAC	AATCACTGCT	300
GACACTTCC	GCAAACTCTT	CCGAGTCTAC	TCCAATTTCC	TCCGGGGAAA	GCTGAAGCTG	360
TACACAGGGG	AGGCCTGCAG	GACAGGGGAC	AGATGAGGCG	GCGGCTCCCC	CCACCACGCC	420
TCATCTGTGA	CAGCCGAGTC	CTGGAGAGGT	ACCTCTTGA	GGCCAAGGAG	GCCGAGAATA	480
TCACGACGGG	CTGTGCTGAA	CACTGCAGCT	TG			512

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

GAGAATATCA	CTGTCCCAGA	CACCAAAGTT	AATTTCTATG	CCTGGAAGAG	GATGGAGGTC	60
GGGCAGCAGG	CCGTAGAAGT	CTGGCAGGGC	CTGGCCCTGC	TGTCGGAAGC	TGTCCTGCGG	120
GGCCAGGCCC	TGTTGGTCAA	CTCTTCCCAG	CCGTGGGAGC	CCCTGCAGCT	GCATGTGGAT	180
AAAGCCGTC	GTGGCCTTCG	CAGCCTCACC	ACTCTGCTTC	GGGCTCTGGG	AGCCCAGAAG	240
GAAGCCATCT	CCCCTCCAGA	TGCGGCCTCA	GCTGCTCCAC	TCCGAACAAT	CACTGCTGAC	300
ACTTTCCGCA	AACCTTCCG	AGTCTACTCC	AATTTCTCC	GGGGAAAGCT	GAAGCTGTAC	360
ACAGGGGAGG	CCTGCAGGAC	AGGGGACAGA	TGAGCGGCG	GCTCCCCCA	CCACGCCTCA	420
TCTGTGACAG	CCGAGTCCTG	GAGAGGTACC	TCTTGGAGGC	CAAGGAGGCC	GAGAATATCA	480
CGACGGGCTG	TGCTGAACAC	TGCAGCTTGA	AT			512

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

AATATCACTG	TCCCAGACAC	CAAAGTTAAT	TTCTATGCCT	GGAAGAGGAT	GGAGGTCGGG	60
CAGCAGGCCG	TAGAAGTCTG	GCAGGGCCTG	GCCCTGCTGT	CGGAAGCTGT	CCTGCGGGGC	120
CAGGCCCTGT	TGGTCAACTC	TTCCCAGCCG	TGGGAGCCCC	TGCAGCTGCA	TGTGGATAAA	180
GCCGTCACTG	GCCTTCGCAG	CCTCACCCT	CTGCTTCGGG	CTCTGGGAGC	CCAGAAGGAA	240
GCCATCTCCC	CTCCAGATGC	GGCCTCAGCT	GCTCCACTCC	GAACAATCAC	TGCTGACACT	300
TTCCGCAAA	TCTTCCGAGT	CTACTCCAAT	TTCTCCGGG	GAAAGCTGAA	GCTGTACACA	360
GGGGAGGCC	GCAGGACAGG	GGACAGATGA	GGCGGCGGCT	CCCCCACC	CGCCTCATCT	420
GTGACAGCCG	AGTCCTGGAG	AGGTACCTCT	TGGAGGCCAA	GGAGGCCGAG	AATATCACGA	480
GGGCTGTGTC	TGAACACTGC	AGCTTGAATG	AG			512

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 512 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

ATCACTGTCC	CAGACACCAA	AGTTAATTTC	TATGCCTGGA	AGAGGATGGA	GGTCGGGCAG	60
CAGGCCGTAG	AAGTCTGGCA	GGGCCTGGCC	CTGCTGTCCG	AAGCTGTCTT	GCGGGGCCAG	120
GCCCTGTGG	TCAACTCTTC	CCAGCCGTGG	GAGCCCCCTG	AGCTGCATGT	GGATAAAGCC	180
GTCAGTGGCC	TTGCGAGCCT	CACCACTCTG	CTTCGGGCTC	TGGGAGCCCC	GAAGGAAGCC	240
ATCTCCCCCT	CAGATGCGGC	CTCAGCTGCT	CCACTCCGAA	CAATCACTGC	TGACACTTTC	300
CGCAAACCT	TCCGAGTCTA	CTCCAATTTC	CTCCGGGGAA	AGCTGAAGCT	GTACACAGGG	360
GAGGCCTGCA	GGACAGGGGA	CAGATGAGGC	GGCGGCTCCC	CCCACCACGC	CTCATCTGTG	420
ACAGCCGAGT	CCTGGAGAGG	TACCTCTTGG	AGGCCAAGGA	GGCCGAGAAT	ATCACGACGG	480
GCTGTGCTGA	ACACTGCAGC	TTGAATGAGA	AT			512

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

ACTGTCCCAG	ACACCAAAGT	TAATTTCTAT	GCCTGGAAGA	GGATGGAGGT	CGGGCAGCAG	60
CCCCTAGAAG	TCTGGCAGGG	CCTGGCCCTG	CTGTCCGAAG	CTGTCTGCG	GGGCCAGGCC	120
CTGTTGGTCA	ACTCTTCCCA	GCCGTGGGAG	CCCCTGCAGC	TGCATGTGGA	TAAAGCCGTC	180

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AGTGGCCTTC	GCAGCCTCAC	CACTCTGCTT	CGGGCTCTGG	GAGCCCAGAA	GGAAGCCATC	240
TCCCCTCCAG	ATGCGGCCTC	AGCTGTCTCA	CTCCGAACAA	TCACTGCTGA	CACTTTCCGC	300
AAACTCTTCC	GAGTCTACTC	CAATTTCTCT	CGGGGAAAGC	TGAAGCTGTA	CACAGGGGAG	360
GCCTGCAGGA	CAGGGGACAG	ATGAGGCGGC	GGCTCCCCCC	ACCACGCCTC	ATCTGTGACA	420
GCCGAGTCCT	GGAGAGGTAC	CTCTTGAGAG	CCAAGGAGGC	CGAGAATATC	ACGACGGGCT	480
GTGCTGAACA	CTGCAGCTTG	AATGAGAATA	ATC			513

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

GTCCCAGACA	CCAAAGTTAA	TTTCTATGCC	TGGAAGAGGA	TGGAGGTCGG	GCAGCAGGCC	60
GTAGAAGTCT	GGCAGGGCCT	GGCCCTGCTG	TGGAAGCTG	TCCTGCGGGG	CCAGGCCCTG	120
TTGGTCAACT	CTTCCAGACC	GTGGGAGCCC	CTGCAGCTGC	ATGTGGATAA	AGCCGTCACT	180
GGCCTTCGCA	GCCTCACCAC	TCTGCTTCGG	GCTCTGGGAG	CCCAGAAGGA	AGCCATCTCC	240
CCTCCAGATG	CGGCCTCAGC	TGCTCCACTC	CGAACAATCA	CTGCTGACAC	TTTCCGCAAA	300
CTCTTCCGAG	TCTACTCCAA	TTTCTCCGGG	GGAAAGCTGA	AGCTGTACAC	AGGGGAGGCC	360
TGCAGGACAG	GGGACAGATG	AGGCGGCGGC	TCCCCCACC	ACGCCTCATC	TGTGACAGCC	420
GAGTCTTGGA	GAGGTACCTC	TTGGAGGCCA	AGGAGGCCGA	GAATATCACG	ACGGGCTGTG	480
CTGAACACTG	CAGCTTGAAT	GAGAATAATC	ACT			513

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

CCAGACACCA	AAGTTAATTT	CTATGCCTGG	AAGAGGATGG	AGGTCGGGCA	GCAGGCCGTA	60
GAAGTCTGGC	AGGGCCTGGC	CCTGCTGTGG	GAAGCTGTCC	TGCGGGGCCA	GGCCCTGTTG	120
GTCAACTCTT	CCCAGCCGTG	GGAGCCCCTG	CAGCTGCATG	TGGATAAAGC	CGTCAGTGGC	180
CTTCGCAGCC	TCACCACTCT	GCTTCGGGCT	CTGGGAGCCC	AGAAGGAAGC	CATCTCCCCT	240
CCAGATGCGG	CCTCAGCTGC	TCCACTCCGA	ACAATCACTG	CTGACACTTT	CCGCAAATC	300
TTCCGAGTCT	ACTCCAATTT	CCTCCGGGGA	AAGCTGAAGC	TGTACACAGG	GGAGGCTG	360
AGGACAGGGG	ACAGATGAGG	CGGCGGCTCC	CCCCACCACG	CCTCATCTGT	GACAGCCGAG	420
TCTTGAGAG	GTACCTCTTG	GAGGCCAAGG	AGGCCGAGAA	TATCACGACG	GGCTGTGCTG	480
AACACTGCAG	CTTGAATGAG	AATAACTACT	GTC			513

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

GACACCAAAG	TTAATTTCTA	TGCCTGGAAG	AGGATGGAGG	TCGGGCAGCA	GGCCGTAGAA	60
GTCTGGCAGG	GCCTGGCCCT	GCTGTGCGAA	GCTGTCTCTG	GGGGCCAGGC	CCTGTTGGTC	120
AACTCTTCCC	AGCCGTGGGA	GCCCCTGCAG	CTGCATGTGG	ATAAAGCCGT	CAGTGGCCTT	180
CGCAGCCTCA	CACTCTGTCT	TCGGGCTCTG	GGAGCCCAGA	AGGAAGCCAT	CTCCCCTCCA	240
GATGCGGCCT	CAGCTGTCTC	ACTCCGAACA	ATCACTGCTG	ACACTTTCCG	CAAACTCTTC	300
CGAGTCTACT	CCAATTTCTT	CCGGGGAAAG	CTGAAGCTGT	ACACAGGGGA	GGCCTGCAGG	360
ACAGGGGACA	GATGAGGCGG	CGGCTCCCCC	CACCACGCCT	CATCTGTGAC	AGCCGACTCC	420
TGGAGAGGTA	CCTCTTGGAG	GCCAAGGAGG	CCGAGAATAT	CACGACGGGC	TGTGCTGAAC	480
ACTGCAGCTT	GAATGAGAAT	AATCACTGTC	CCA			513

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

AGGATGGAGG	TCGGGCAGCA	GGCCGTAGAA	GTCTGGCAGG	GCCTGGCCCT	GCTGTCGGAA	60
GCTGTCTGCG	GGGGCCAGGC	CCTGTTGGTC	AACTCTTCCC	AGCCGTGGGA	GCCCCTGCAG	120
CTGCATGTGG	ATAAAGCCGT	CAGTGGCCTT	CGCAGCCTCA	CCACTCTGCT	TCGGGCTCTG	180
GGAGCCCAGA	AGGAAGCCAT	CTCCCTCCCA	GATGCGGCCT	CAGCTGTCTC	ACTCCGAACA	240
ATCACTGCTG	ACACTTTCCG	CAAACTCTTC	CGAGTCTACT	CCAATTTCTT	CCGGGGAAAG	300
CTGAAGCTGT	ACACAGGGGA	GGCCTGCAGG	ACAGGGGACA	GATGAGGCGG	CGGCTCCCCC	360
CACCACGCC	CATCTGTGAC	AGCCGAGTCC	TGGAGAGGTA	CCTCTTGGAG	GCCAAGGAGG	420
CCGAGAATAT	CACGACGGGC	TGTGCTGAAC	ACTGCAGCTT	GAATGAGAAT	AATCACTGTC	480
CCAGACACCA	AAGTTAATT	CTATGCCTGG	AAG			513

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

ATGGAGGTCG	GGCAGCAGGC	CGTAGAAGTC	TGGCAGGGCC	TGGCCCTGCT	GTCGGAAGCT	60
GTCTTGCGGG	GCCAGGCCCT	GTTGGTCAAC	TCTTCCCAGC	CGTGGGAGCC	CCTGCAGCTG	120
CATGTGGATA	AAGCCGTACG	TGGCCTTCGC	AGCCTCACCA	CTCTGCTTCG	GGCTCTGGGA	180
GCCCAGAAAG	AAGCCATCTC	CCCTCCAGAT	GCGGCCTCAG	CTGCTCCACT	CCGAACAATC	240
ACTGCTGACA	CTTTCGCGAA	ACTCTTCCGA	GTCTACTCCA	ATTTCCTCCG	GGGAAAGCTG	300
AAGCTGTACA	CAGGGGAGGC	CTGCAGGACA	GGGGACAGAT	GAGGCGGCGG	CTCCCCCAC	360
CACGCCTCAT	CTGTGACAGC	CGAGTCCTGG	AGAGGTACCT	CTTGGAGGCC	AAGGAGGCCG	420
AGAATATCAC	GACGGGCTGT	GCTGAACACT	GCAGCTTGAA	TGAGAATAAT	CACGTGCCCA	480
GACACCAAAG	TTAATTTCTA	TGCCTGGAAG	AGG			513

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

GAGGTCGGGC	AGCAGGCCGT	AGAAGTCTGG	CAGGGCCTGG	CCCTGCTGTC	GGAAGCTGTC	60
CTGCGGGGCC	AGGCCCTGTT	GGTCAACTCT	TCCAGCCGT	GGGAGCCCT	GCAGCTGCAT	120
GTGGATAAAG	CCGTCACTGG	CCTTCGCAGC	CTCACCCTC	TGCTTCGGGC	TCTGGGAGCC	180
CAGAAGGAAG	CCATCTCCCC	TCCAGATGCG	GCCTCAGCTG	CTCCACTCCG	AACAATCACT	240
GCTGACACTT	TCCGCAAAT	CTTCCGAGTC	TACTCCAATT	TCCTCCGGGG	AAAGCTGAAG	300
CTGTACACAG	GGGAGGCCTG	CAGGACAGGG	GACAGATGAG	GCGGCGGCTC	CCCCCACCAC	360
GCCTCATCTG	TGACAGCCGA	GTCTCGGAGA	GGTACCTCTT	GGAGGCCAAG	GAGGCCGAGA	420
ATATCACGAC	GGGCTGTGCT	GAACACTGCA	GCTTGAATGA	GAATAATCAC	TGTCCAGAC	480
ACCAAAGTTA	ATTCTATGCT	CTGGAAGAGG	ATG			513

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

GTGCGGCAGC	AGGCCGTAGA	AGTCTGGCAG	GGCCTGGCCC	TGCTGTCCGA	AGCTGTCTCTG	60
CGGGGCCAGG	CCCTGTTGGT	CAACTCTTCC	CAGCCGTGGG	AGCCCTTGCA	GCTGCATGTG	120
GATAAAGCCG	TCAGTGGCCT	TCGCAGCCTC	ACCACTCTGC	TTCGGGCTCT	GGGAGCCAG	180
AAGGAAGCCA	TCTCCCCTCC	AGATGCGGCC	TCAGCTGCTC	CACTCCGAAC	AATCACTGCT	240
GACACTTTCC	GCAAACTCTT	CCGAGTCTAC	TCCAATTCTC	TCCGGGGAAA	GCTGAAGCTG	300
TACACAGGGG	AGGCCTGCAG	GACAGGGGAC	AGATGAGGCG	GCGGCTCCCC	CCACCACGCC	360
TCATCTGTGA	CAGCCGAGTC	CTGGAGAGGT	ACCTCTTGGA	GGCCAAGGAG	GCCGAGAATA	420
TCACGACGGG	CTGTGCTGAA	CACTGCAGCT	TGAATGAGAA	TAATCACTGT	CCCAGACACC	480
AAAGTTAATT	TCTATGCCTG	GAAGAGGATG	GAG			513

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

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CAGGCCCTGT TGGTCAACTC TTCCAGCCG TGGGAGCCCC TGCAGCTGCA TGTGGATAAA    60
GCCGTCAGTG GCCTTCGCAG CCTCACCAC CTGCTTCGGG CTCTGGGAGC CCAGAAGGAA    120
GCCATCTCCC CTCAGATGC GGCCTCAGCT GCTCCACTCC GAACAATCAC TGCTGACACT    180
TTCCGAAAC TCTTCGAGT CTACTCCAAT TTCCTCCGGG GAAAGCTGAA GCTGTACACA    240
GGGGAGGCCT GCAGGACAGG GGACAGATGA GCGGCGGGCT CCCCCACCA CGCTCATCT    300
GTGACAGCCG AGTCCTGGAG AGGTACCTCT TGGAGGCCAA GGAGGCCGAG AATATCAGCA    360
CGGGCTGTGC TGAACACTGC AGCTTGAATG AGAATAATCA CTGTCCCAGA CACCAAAGTT    420
AATTTCTATG CCTGGAAGAG GATGGAGGTC GGGCAGCAGG CCGTAGAAGT CTGGCAGGGC    480
CTGGCCCTGC TGTCGGAAGC TGTCCTGCGG GGC                                     513

```

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

```

GCCCTGTTGG TCAACTCTTC CCAGCCGTGG GAGCCCTGCG AGCTGCATGT GGATAAAGCC    60
GTCAGTGGCC TTGCGAGCCT CACCACTCTG CTTCGGGCTC TGGGAGCCCA GAAGGAAGCC    120
ATCTCCCCTC CAGATGCGGC CTCAGCTGCT CCACTCCGAA CAATCACTGC TGACACTTTC    180
CGCAAATCTT TCCGAGTCTA CTCCAATTTC CTCCGGGGAA AGCTGAAGCT GTACACAGGG    240
GAGGCCTGCA GGACAGGGGA CAGATGAGGC GCGGCTCCC CCCACCACGC CTCATCTGTG    300
ACAGCCGAGC CTGGAGAGG TACCTCTTGG AGGCCAAGGA GGCCGAGAAT ATCAGCACGG    360
GCTGTGCTGA ACACTGCAGC TTGAATGAGA ATAATCACTG TCCCAGACAC CAAAGTTAAT    420
TTCTATGCCT GGAAGAGGAT GGAGGTCGGG CAGCAGGCCG TAGAAGTCTG GCAGGGCCTG    480
GCCCTGCTGT CGGAAGCTGT CCTCGGGGGC CAG                                     513

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(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

```

CTGTTGGTCA ACTCTTCCCA GCCGTGGGAG CCCCTGCAGC TGCATGTGGA TAAAGCCGTC    60
AGTGGCCCTC GCAGCCTCAC CACTCTGCTT CGGGCTCTGG GAGCCCAGAA GGAAGCCATC    120
TCCCCTCCAG ATGCGGCCTC AGCTGCTCCA CTCCGAACAA TCACTGCTGA CACTTTCGCG    180
AAACTCTTCC GAGTCTACTC CAATTTCCTC CGGGGAAAGC TGAAGCTGTA CACAGGGGAG    240
GCCTGCAGGA CAGGGGACAG ATGAGGCGGC GGCTCCCCC ACCACGCCTC ATCTGTGACA    300
GCCGAGTCCT GGAGAGGTAC CTCTTGAGG CCAAGGAGGC CGAGAATATC ACGACGGGCT    360
GTGCTGAACA CTGCAGCTTG AATGAGAATA ATCACTGTCC CAGACACCAA AGTTAATTTT    420
TATGCCCTGA AGAGGATGGA GGTGCGGCAG CAGGCCGTAG AAGTCTGGCA GGGCCTGGCC    480
CTGCTGTCGG AAGCTGTCTT GCGGGGCCAG GCC                                     513

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(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```

TTGGTCAACT CTTCCAGACC GTGGGAGCCC CTGCAGCTGC ATGTGGATAA AGCCGTCAGT    60
GGCCTTCGCA GCCTCACCAC TCTGCTTCGG GCTCTGGGAG CCCAGAAGGA AGCCATCTCC    120
CCTCCAGATG CGGCCTCAGC TGCTCCACTC CGAACAATCA CTGCTGACAC TTTCGCAAA    180

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CTCTTCCGAG	TCTACTCCAA	TTTCCTCCGG	GGAAAGCTGA	AGCTGTACAC	AGGGGAGGCC	240
TGCAGGACAG	GGGACAGATG	AGGCGGCGGC	TCCCCCACC	ACGCCTCATC	TGTGACAGCC	300
GAGTCCTGGA	GAGGTACCTC	TTGGAGGCCA	AGGAGGCCGA	GAATATCACG	ACGGGCTGTG	360
CTGAACACTG	CAGCTTGAAT	GAGAATAATC	ACTGTCCCAG	ACACCAAAGT	TAATTCTAT	420
GCCTGGAAGA	GGATGGAGGT	CGGGCAGCAG	GCCGTAGAAG	TCTGGCAGGG	CCTGGCCCTG	480
CTGTCCGAAG	CTGTCTGCG	GGGCCAGGCC	CTG			513

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

GTCAACTCTT	CCCAGCCGTG	GGAGCCCCTG	CAGCTGCATG	TGGATAAAGC	CGTCAGTGGC	60
CTTCGCAGCC	TCACCACTCT	GCTTCGGGCT	CTGGGAGCCC	AGAAGGAAGC	CATCTCCCTT	120
CCAGATGCGG	CCTCAGCTGC	TCCACTCCGA	ACAATCACTG	CTGACACTTT	CCGCAAACCTC	180
TTCCGAGTCT	ACTCCAATTT	CCTCCGGGGA	AAGCTGAAGC	TGTACACAGG	GGAGGCCTGC	240
AGGACAGGGG	ACAGATGAGG	CGGCGGCTCC	CCCCACCACG	CCTCATCTGT	GACAGCCGAG	300
TCCTGGAGAG	GTACCTCTTG	GAGGCCAAGG	AGGCCGAGAA	TATCAGCAGC	GGCTGTGCTG	360
AACACTGCAG	CTTGAATGAG	AATAATCACT	GTCCCAGACA	CCAAAGTTAA	TTTCTATGCC	420
TGGAAGAGGA	TGGAGGTCGG	GCAGCAGGCC	GTAGAAGTCT	GGCAGGCGCT	GGCCCTGCTG	480
TCGGAAGCTG	TCCTGCGGGG	CCAGGCCCTG	TTG			513

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

AACTCTTCCC	AGCCGTGGGA	GGCCCTGCAG	CTGCATGTGG	ATAAAGCCGT	CAGTGGCCTT	60
CGCAGCCTCA	CCACTCTGCT	TCGGGCTCTG	GGAGCCCAGA	AGGAAGCCAT	CTCCCCTCCA	120
GATGCGGCCCT	CAGCTGCTCC	ACTCCGAACA	ATCACTGCTG	ACACTTTCCG	CAAACCTCTTC	180
CGAGTCTACT	CCAATTTCCCT	CCGGGGAAAG	CTGAAGCTGT	ACACAGGGGA	GGCCTGCAGG	240
ACAGGGGACA	GATGAGGCGG	CGGCTCCCCC	CACCACGCCT	CATCTGTGAC	AGCCGAGTCC	300
TGGAGAGGTA	CCTCTTGAGG	GCCAAGGAGG	CCGAGAATAT	CACGACGGGC	TGTGCTGAAC	360
ACTGCAGCTT	GAATGAGAAT	AATCACTGTC	CCAGACACCA	AAGTTAATTT	CTATGCCTGG	420
AAGAGGATGG	AGGTCGGGCA	GCAGGCCGTA	GAAGTCTGGC	AGGGCCTGGC	CCTGTCTGTCG	480
GAAGCTGTCC	TGCGGGGCCA	GGCCCTGTTG	GTC			513

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

TCTTCCAGC	CGTGGGAGCC	CCTGCAGCTG	CATGTGGATA	AAGCCGTGAG	TGGCCTTCGC	60
AGCCTCACCA	CTCTGCTTCG	GGCTCTGGGA	GCCCAGAAGG	AAGCCATCTC	CCCTCCAGAT	120
GCGGCCTCAG	CTGCTCCACT	CCGAACAATC	ACTGCTGACA	CTTTCCGCAA	ACTCTTCCGA	180
GTCTACTCCA	ATTTCTCTCG	GGGAAAGCTG	AAGCTGTACA	CAGGGGAGGC	CTGCAGGACA	240
GGGGACAGAT	GAGGCGGCGG	CTCCCCCAC	CACGCCTCAT	CTGTGACAGC	CGAGTCCTGG	300
AGAGGTACCT	CTTGGAGGCC	AAGGAGGCCG	AGAATATCAC	GACGGGCTGT	GCTGAACACT	360
GCAGCTTGAA	TGAGAATAAT	CACGTGCCCA	GACACCAAAG	TTAATTTCTA	TGCCTGGAAG	420
AGGATGGAGG	TCGGGCAGCA	GGCCGTAGAA	GTCTGGCAGG	GCCTGGCCCT	GCTGTGCGAA	480
GCTGTCTGTC	GGGGCCAGGC	CCTGTTGGTC	AAC			513

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

TCCCAGCCGT	GGGAGCCCCT	GCAGCTGCAT	GTGGATAAAG	CCGTCAGTGG	CCTTCGCAGC	60
CTCACCACCTC	TGCTTCGGGC	TCTGGGAGCC	CAGAAGGAAG	CCATCTCCCC	TCCAGATGCG	120
GCCTCAGCTG	CTCCACTCCG	AACAATCACT	GCTGACACTT	TCCGCAAAC	CTTCCGAGTC	180
TACTCCAATT	TCCTCCGGGG	AAAGCTGAAG	CTGTACACAG	GGGAGGCCTG	CAGGACAGGG	240
GACAGATGAG	GCGGCGGCTC	CCCCCACCAC	GCCTCATCTG	TGACAGCCGA	GTCCTGGAGA	300
GGTACCTCTT	GGAGGCCAAG	GAGGCCGAGA	ATATCACGAC	GGGCTGTGCT	GAACACTGCA	360
GCTTGAATGA	GAATAATCAC	TGTCCCAGAC	ACCAAAGTTA	ATTTCTATGC	CTGGAAGAGG	420
ATGGAGGTCG	GGCAGCAGGC	CGTAGAAGTC	TGGCAGGGCC	TGGCCCTGCT	GTCCGAAGCT	480
GTCTTCGGGG	GCCAGGCCCT	GTTGGTCAAC	TCT			513

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

CAGCCGTGGG	AGCCCTTGCA	GCTGCATGTG	GATAAAGCCG	TCAGTGGCCT	TCGCAGCCTC	60
ACCACTCTGC	TTCGGGCTCT	GGGAGCCCAG	AAGGAAGCCA	TCTCCCTCC	AGATGCGGCC	120
TCAGTGCTC	CACTCCGAAC	AATCACTGCT	GACACTTTCC	GCAAACTCTT	CCGAGTCTAC	180
TCCAATTTC	TCCGGGGAAA	GCTGAAGCTG	TACACAGGGG	AGGCCTGCAG	GACAGGGGAC	240
AGATGAGGCG	GCGGCTCCCC	CCACCACGCC	TCATCTGTGA	CAGCCGAGTC	CTGGAGAGGT	300
ACCTCTTGGA	GGCCAAGGAG	GCCGAGAATA	TCACGACGGG	CTGTGCTGAA	CACTGCAGCT	360
TGAATGAGAA	TAATCACTGT	CCCAGACACC	AAAGTTAATT	TCTATGCCCTG	GAAGAGGATG	420
GAGGTCGGGC	AGCAGGCCGT	AGAAGTCTGG	CAGGGCCTGG	CCCTGCTGTC	GGAAGCTGTC	480
CTGCGGGGCC	AGGCCTGTT	GGTCAACTCT	TCC			513

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

CCGTGGGAGC	CCCTGCAGCT	GCATGTGGAT	AAAGCCGTCA	GTGGCCTTCG	CAGCCTCACC	60
ACTCTGCTTC	GGGCTCTGGG	AGCCCAGAAG	GAAGCCATCT	CCCTCCAGA	TGCGGCCTCA	120
GCTGCTCCAC	TCCGAACAAT	CACTGCTGAC	ACTTTCCGCA	AACTCTTCG	AGTCTACTCC	180
AATTTCTCTC	GGGGAAAGCT	GAAGCTGTAC	ACAGGGGAGG	CCTGCAGGAC	AGGGGACAGA	240
TGAGGCGGCG	GCTCCCCCA	CCACGCCTCA	TCTGTGACAG	CCGAGTCTCTG	GAGAGGTACC	300
TCTTGAGGCG	CAAGGAGGCC	GAGAATATCA	CGACGGGCTG	TGCTGAACAC	TGCAGCTTGA	360
ATGAGAATAA	TCACTGTCCC	AGACACCAA	GTTAATTCT	ATGCCTGGAA	GAGGATGGAG	420
GTCGGGCAGC	AGGCCGTAGA	AGTCTGGCAG	GCCCTGGCCC	TGCTGTCCGA	AGCTGTCTCTG	480
CGGGGCCAGG	CCCTGTTGGT	CAACTCTTCC	CAG			513

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

TGGGAGCCCC	TGCAGCTGCA	TGTGGATAAA	GCCGTCACTG	GCCTTCGCAG	CCTCACCAC	60
CTGCTTCGGG	CTCTGGGAGC	CCAGAAGGAA	GCCATCTCCC	CTCCAGATGC	GGCCTCAGCT	120
GCTCCACTCC	GAACAATCAC	TGCTGACACT	TTCCGCAAAC	TCTTCCGAGT	CTACTCCAAT	180
TTCCTCCGGG	GAAAGCTGAA	GCTGTACACA	GGGGAGGCCT	GCAGGACAGG	GGACAGATGA	240
GGCGGGGGCT	CCCCCACCAC	CGCCTCATCT	GTGACAGCCG	AGTCCTGGAG	AGGTACCTCT	300
TGGAGGCCAA	GGAGGCCGAG	AATATCACGA	CGGGCTGTGC	TGAACACTGC	AGCTTGAATG	360
AGAATAATCA	CTGTCCCAGA	CACCAAAGTT	AATTTCTATG	CCTGGAAGAG	GATGGAGGTC	420
GGGCAGCAGG	CCGTAGAAGT	CTGGCAGGGC	CTGGCCCTGC	TGTCGGAAGC	TGTCCTGCGG	480
GGCCAGGCC	TGTTGGTCAA	CTCTTCCCAG	CCG			513

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(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

GAGCCCCTGC	AGCTGCATGT	GGATAAAGCC	GTCACTGGCC	TTCGCAGCCT	CACCACTCTG	60
CTTCGGGCTC	TGGGAGCCCA	GAAGGAAGCC	ATCTCCCCTC	CAGATGCGGC	CTCAGCTGCT	120
CCACTCCGAA	CAATCACTGC	TGACACTTTC	CGCAAACCTC	TCCGAGTCTA	CTCCAATTTC	180
CTCCGGGGAA	AGCTGAAGCT	GTACACAGGG	GAGGCCTGCA	GGACAGGGGA	CAGATGAGGC	240
GGCGGCTCCC	CCCACCACGC	CTCATCTGTG	ACAGCCGAGT	CCTGGAGAGG	TACCTCTTGG	300
AGGCCAAGGA	GGCCGAGAAT	ATCACGACGG	GCTGTGCTGA	ACACTGCAGC	TTGAATGAGA	360
ATAATCACTG	TCCCAGACAC	CAAAGTTAAT	TTCTATGCCT	GGAAGAGGAT	GGAGGTCGGG	420
CAGCAGGCCG	TAGAACTCTG	GCAGGGCCTG	GCCCTGCTGT	CGGAAGCTGT	CCTGCGGGGC	480
CAGGCCCTGT	TGGTCAACTC	TTCCAGCCG	TGG			513

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

CTTCGGGCTC	TGGGAGCCCA	GAAGGAAGCC	ATCTCCCCTC	CAGATGCGGC	CTCAGCTGCT	60
CCACTCCGAA	CAATCACTGC	TGACACTTTC	CGCAAACCTC	TCCGAGTCTA	CTCCAATTTC	120
CTCCGGGGAA	AGCTGAAGCT	GTACACAGGG	GAGGCCTGCA	GGACAGGGGA	CAGATGAGGC	180
GGCGGCTCCC	CCCACCACGC	CTCATCTGTG	ACAGCCGAGT	CCTGGAGAGG	TACCTCTTGG	240
AGGCCAAGGA	GGCCGAGAAT	ATCACGACGG	GCTGTGCTGA	ACACTGCAGC	TTGAATGAGA	300
ATAATCACTG	TCCCAGACAC	CAAAGTTAAT	TTCTATGCCT	GGAAGAGGAT	GGAGGTCGGG	360
CAGCAGGCCG	TAGAACTCTG	GCAGGGCCTG	GCCCTGCTGT	CGGAAGCTGT	CCTGCGGGGC	420
CAGGCCCTGT	TGGTCAACTC	TTCCAGCCG	TGGGAGCCCC	TGCAGCTGCA	TGTGGATAAA	480
GCCGTCAGTG	GCCTTCGCAG	CCTCACCACT	CTG			513

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

CGGGCTCTGG	GAGCCCAGAA	GGAAGCCATC	TCCCCTCCAG	ATGCGGCCTC	AGCTGCTCCA	60
CTCCGAACAA	TCACTGCTGA	CACTTTCGCG	AAACTCTTCC	GAGTCTACTC	CAATTTCCTC	120
CGGGGAAAGC	TGAAGCTGTA	CACAGGGGAG	GCCTGCAGGA	CAGGGGACAG	ATGAGGCGGC	180
GGCTCCCCCC	ACCACGCCTC	ATCTGTGACA	GCCGAGTCCT	GGAGAGGTAC	CTCTTGGAGG	240
CCAAGGAGGC	CGAGAATATC	ACGACGGGCT	GTGCTGAACA	CTGCAGCTTG	AATGAGAATA	300
ATCACTGTCC	CAGACACCAA	AGTTAATTTC	TATGCCTGGA	AGAGGATGGA	GGTCGGGCAG	360
CAGGCCGCTAG	AAGTCTGGCA	GGGCCTGGCC	CTGCTGTCGG	AAGCTGTCTC	GCGGGGCCAG	420
GCCTGTTGG	TCAACTCTTC	CCAGCCGTGG	GAGCCCCTGC	AGCTGCATGT	GGATAAAGCC	480
GTCAGTGGCC	TTCGCAGCCT	CACCACTCTG	CTT			513

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

GCTCTGGGAG	CCCAGAAGGA	AGCCATCTCC	CCTCCAGATG	CGGCCTCAGC	TGCTCCACTC	60
CGAACAATCA	CTGCTGACAC	TTTCCGCAAA	CTCTTCCGAG	TCTACTCCAA	TTTCTCCGG	120
GGAAAGCTGA	AGCTGTACAC	AGGGGAGGCC	TGCAGGACAG	GGGACAGATG	AGGCGGCGGC	180

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TCCCCCACC	ACGCCTCATC	TGTGACAGCC	GAGTCCTGGA	GAGGTACCTC	TTGGAGGCCA	240
AGGAGGCCCA	GAATATCACG	ACGGGCTGTG	CTGAACACTG	CAGCTTGAAT	GAGAATAATC	300
ACTGTCCCAG	ACACCAAAGT	TAATTTCTAT	GCCTGGAAGA	GGATGGAGGT	CGGGCAGCAG	360
GCCGTAGAAG	TCTGGCAGGG	CCTGGCCCTG	CTGTCGGAAG	CTGTCTGCG	GGGCCAGGCC	420
CTGTTGGTCA	ACTCTTCCCA	GCCGTGGGAG	CCCCTGCAGC	TGCATGTGGA	TAAAGCCGTC	480
AGTGGCCTTC	GCAGCCTCAC	CACTCTGCTT	CGG			513

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

CTGGGAGCCC	AGAAGGAAGC	CATCTCCCCT	CCAGATGCGG	CCTCAGCTGC	TCCACTCCGA	60
ACAATCACTG	CTGACACTTT	CCGCAAACTC	TTCCGAGTCT	ACTCCAATTT	CCTCCGGGGG	120
AAGCTGAAGC	TGTACACAGG	GGAGGCCTGC	AGGACAGGGG	ACAGATGAGG	CGGCGGCTCC	180
CCCCACCACG	CCTCATCTGT	GACAGCCGAG	TCCTGGAGAG	GTACCTCTTG	GAGGCCAAGG	240
AGGCCGAGAA	TATCACGACG	GGCTGTGCTG	AACACTGCAG	CTTGAATGAG	AATAATCACT	300
GTTCCAGACA	CCAAAGTTAA	TTTCTATGCG	TGGAAGAGGA	TGGAGGTCCG	GCAGCAGGCC	360
GTAGAAGTCT	GGCAGGGCCT	GGCCCTGCTG	TCGGAAGCTG	TCTGCGGGGG	CCAGGCCCTG	420
TTGGTCAAAT	CTTCCCAGCC	GTGGGAGCCC	CTGCAGCTGC	ATGTGGATAA	AGCCGTCAGT	480
GGCCTTCGCA	GCCTCACCAC	TCTGCTTCGG	GTC			513

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

GGAGCCCAGA	AGGAAGCCAT	CTCCCCCTCA	GATGCGGCCT	CAGCTGCTCC	ACTCCGAACA	60
ATCACTGCTG	ACACTTTCCG	CAAACCTCTC	CGAGTCTACT	CCAATTTCTT	CCGGGGAAAG	120
CTGAAGCTGT	ACACAGGGGA	GGCCTGCAGG	ACAGGGGACA	GATGAGGCGG	CGGCTCCCCC	180
CACCACGCCT	CATCTGTGAC	AGCCGAGTCC	TGGAGAGGTA	CCTCTTGGAG	GCCAAGGAGG	240
CCGAGAAATAT	CACGACGGGC	TGTGCTGAAC	ACTGCAGCTT	GAATGAGAAT	AATCACTGTC	300
CCAGACACCA	AAGTTAATTT	CTATGCCTGG	AAGAGGATGG	AGGTCGGGCA	GCAGGCCGTA	360
GAAGTCTGGC	AGGGCCTGGC	CCTGCTGTGC	GAAGCTGTCC	TGCGGGGGCA	GGCCCTGTTG	420
GTCAACTCTT	CCAGCCCGTG	GGAGCCCTG	CAGCTGCATG	TGGATAAAGC	CGTCAGTGGC	480
CTTCGCAGCC	TCACCACTCT	GCTTCGGGCT	CTG			513

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

GCCCAGAAGG	AAGCCATCTC	CCCTCCAGAT	GCGGCCTCAG	CTGCTCCACT	CCGAACAATC	60
ACTGCTGACA	CTTCCGCAAA	ACTCTTCCGA	GTCTACTCCA	ATTTCTCTCG	GGGAAAGCTG	120
AAGCTGTACA	CAGGGGAGGC	CTGCAGGACA	GGGGACAGAT	GAGGCGGCGG	CTCCCCCCAC	180
CACGCCTCAT	CTGTGACAGC	CGAGTCCTGG	AGAGGTACCT	CTTGGAGGCC	AAGGAGGCCG	240
AGAATATCAC	GACGGGCTGT	GCTGAACACT	GCAGCTTGAA	TGAGAATAAT	CACTGTCCCC	300
GACACCAAAG	TTAATTTCTA	TGCCTGGAAG	AGGATGGAGG	TCGGGCAGCA	GGCCGTAGAA	360
GTCTGGCAGG	GCCTGGCCCT	GCTGTGCGAA	GCTGTCTGTC	GGGGCCAGGC	CCTGTTGGTC	420
AACTCTTCCC	AGCCGTGGGA	GCCCCGTCAG	CTGCATGTGG	ATAAAGCCGT	CAGTGGCCCT	480
CGCAGCCTCA	CCACTCTGCT	TCGGGCTCTG	GGA			513

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

CAGAAGGAAG	CCATCTCCCC	TCCAGATGCG	GCCTCAGCTG	CTCCACTCCG	AACAATCACT	60
GCTGACACTT	TCCGCAAAC	CTTCCGAGTC	TACTCCAATT	TCCTCCGGGG	AAAGCTGAAG	120
CTGTACACAG	GGGAGGCCCT	CAGGACAGGG	GACAGATGAG	GCGGCGGCTC	CCCCCACCAC	180
GCCTCATCTG	TGACAGCCGA	GTCCTGGAGA	GGTACCTCTT	GGAGGCCAAG	GAGGCCGAGA	240
ATATCACGAC	GGGCTGTGCT	GAACACTGCA	GCTTGAATGA	GAATAATCAC	TGTCCCAGAC	300
ACCAAAGTTA	ATTCTATGC	CTGGAAGAGG	ATGGAGGTCG	GGCAGCAGGC	CGTAGAAGTC	360
TGGCAGGGCC	TGGCCCTGCT	GTCGGAAGCT	GTCCTGCGGG	GCCAGGCCCT	GTTGGTCAAC	420
TCTTCCCAGC	CGTGGGAGCC	CCTGCAGCTG	CATGTGGATA	AAGCCGTCAG	TGGCCTTCGC	480
AGCCTCACCA	CTCTGCTTCG	GGCTCTGGGA	GCC			513

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

AAGGAAGCCA	TCTCCCTCC	AGATGCGGCC	TCAGCTGCTC	CACTCCGAAC	AATCACTGCT	60
GACACTTTCC	GCAAACCTT	CCGAGTCTAC	TCCAATTTC	TCCGGGAAA	GCTGAAGCTG	120
TACACAGGGG	AGGCCTGCAG	GACAGGGGAC	AGATGAGGCG	GCGGCTCCCC	CCACCACGCC	180
TCATCTGTGA	CAGCCGAGTC	CTGGAGAGGT	ACCTCTTGGA	GGCCAAGGAG	GCCGAGAATA	240
TCACGACGGG	CTGTGCTGAA	CACTGCAGCT	TGAATGAGAA	TAATCACTGT	CCCAGACACC	300
AAAGTTAATT	TCTATGCCTG	GAAGAGGATG	GAGGTCGGGC	AGCAGGCCGT	AGAAGTCTGG	360
CAGGGCCCTGG	CCCTGCTGTC	GGAAGCTGTC	CTGCGGGGCC	AGGCCCTGTT	GGTCAACTCT	420
TCCAGCCCGT	GGGAGCCCCT	GCAGCTGCAT	GTGGATAAAG	CCGTCAGTGG	CCTTCGCAGC	480
CTCACCACCTC	TGCTTCGGGC	TCTGGGAGCC	CAG			513

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

GAAGCCATCT	CCCCTCCAGA	TGCGGCCTCA	GCTGCTCCAC	TCCGAACAAT	CACTGCTGAC	60
ACTTTCGCCA	AACTCTTCCG	AGTCTACTCC	AATTTCTCCT	GGGGAAAGCT	GAAGCTGTAC	120
ACAGGGGAGG	CCTGCAGGAC	AGGGGACAGA	TGAGGCGGCG	GCTCCCCCA	CCACGCCTCA	180
TCTGTGACAG	CCGAGTCTCT	GAGAGGTACC	TCTTGGAGGC	CAAGGAGGCC	GAGAAATATCA	240
CGACGGGGCTG	TGCTGAACAC	TGCAGCTTGA	ATGAGAATAA	TCACTGTCCC	AGACACCAAA	300
GTTAATTTCT	ATGCCTGGAA	GAGGATGGAG	GTCGGGCAGC	AGGCCGTAGA	AGTCTGGCAG	360
GGCCTGGGCT	TGCTGTGGGA	AGCTGTCTCT	CGGGGCCAGG	CCCTGTTGGT	CAACTCTTCC	420
CAGCCGTGGG	AGCCCTGCA	GCTGCATGTG	GATAAAGCCG	TCAGTGGCCT	TGCAGCCCTC	480
ACCACTCTGC	TTCCGGCTCT	GGGAGCCAG	AAG			513

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

GCCATCTCCC	CTCCAGATGC	GGCCTCAGCT	GCTCCACTCC	GAACAATCAC	TGCTGACACT	60
TTCCGCAAA	TCTTCCGAGT	CTACTCCAAT	TTCTCCGGG	GAAAGCTGAA	GCTGTACACA	120
GGGAGGCCCT	GCAGGACAGG	GGACAGATGA	GGCGGCGGCT	CCCCCACC	CGCCTCATCT	180
GTGACAGCCG	AGTCTGGAG	AGGTACCTCT	TGGAGGCCAA	GGAGGCCGAG	AATATCACGA	240
CGGGCTGTGC	TGAACACTGC	AGCTTGAATG	AGAATAATCA	CTGTCCCAGA	CACCAAAGTT	300
AATTTCTATG	CCTGGAAGAG	GATGGAGGTC	GGGCAGCAGG	CCGTAGAAGT	CTGGCAGGGC	360
CTGGCCCTGC	TGTCGGAAGC	TGTCCTCGCG	GGCCAGGCC	TGTTGGTCAA	CTCTTCCCAG	420
CCGTGGGAGC	CCCTGCAGCT	GCATGTGGAT	AAAGCCGTCA	GTGGCCTTCG	CAGCCTCACC	480
ACTCTGCTTC	GGGCTCTGGG	AGCCCAGAAG	GAA			513

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(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

ATCTCCCTC	CAGATGCGGC	CTCAGCTGCT	CCACTCCGAA	CAATCACTGC	TGACACTTTC	60
CGCAAATCT	TCCGAGTCTA	CTCCAATTTC	CTCCGGGGAA	AGCTGAAGCT	GTACACAGGG	120
GAGGCCGTGA	GGACAGGGGA	CAGATGAGGC	GGCGGCTCCC	CCCACCACGC	CTCATCTGTG	180
ACAGCCGAGT	CCTGGAGAGG	TACCTCTTGG	AGGCCAAGGA	GGCCGAGAAT	ATCACGACGG	240
GCTGTGCTGA	ACACTGCAGC	TTGAATGAGA	ATAATCACTG	TCCCAGACAC	CAAAGTTAAT	300
TTCTATGCCT	GGAAGAGGAT	GGAGGTCGGG	CAGCAGGCCG	TAGAAGCTG	GCAGGGCCTG	360
GCCCTGCTGT	CGGAAGCTGT	CCTGCGGGGC	CAGGCCCTGT	TGGTCAACTC	TTCCCAGCCG	420
TGGGAGCCCC	TGCAGCTGCA	TGTGGATAAA	GCCGTCAGTG	GCCTTCGCAG	CCTCACCAC	480
CTGCTTCGGG	CTCTGGGAGC	CCAGAAGGAA	GCC			513

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

TCCCCTCCAG	ATCGGCCTC	AGCTGCTCCA	CTCCGAACAA	TCACTGCTGA	CACTTTCGCG	60
AAACTCTTCC	GAGTCTACTC	CAATTTCCTC	CGGGGAAAGC	TGAAGCTGTA	CACAGGGGAG	120
GCCTGCAGGA	CAGGGGACAG	ATGAGGCGGC	GGCTCCCCC	ACCACGCCTC	ATCTGTGACA	180
GCCGAGTCCT	GGAGAGGTAC	CTCTTGAGG	CCAAGGAGGC	CGAGAATATC	ACGACGGGCT	240
GTGCTGAACA	CTGCAGCTTG	AATGAGAATA	ATCACTGTCC	CAGACACCAA	AGTTAATTTT	300
TATGCCTGGA	AGAGGATGGA	GGTCGGGCAG	CAGGCCGTAG	AAGTCTGGCA	GGGCCTGGCC	360
CTGCTGTGCG	AAGCTGTCTC	GCGGGGCCAG	GCCCTGTTGG	TCAACTCTTC	CCAGCCGTGG	420
GAGCCCCCTG	AGCTGCATGT	GGATAAAGCC	GTCAGTGGCC	TTCGCAGCCT	CACCACTCTG	480
CTTCGGGCTC	TGGGAGCCCA	GAAGGAAGCC	ATC			513

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

CCTCCAGATG	CGGCCTCAGC	TGCTCCACTC	CGAACAATCA	CTGCTGACAC	TTTCCGCAAA	60
CTCTTCCGAG	TCTACTCCAA	TTTCCTCCGG	GGAAAGCTGA	AGCTGTACAC	AGGGGAGGCC	120
TGCAGGACAG	GGGACAGATG	AGGCGGCGGC	TCCCCCACC	ACGCCTCATC	TGTGACAGCC	180
GAGTCTCTGA	GAGGTACCTC	TTGGAGGCCA	AGGAGGCCGA	GAATATCACG	ACGGGCTGTG	240
CTGAACACTG	CAGCTTGAAT	GAGAATAATC	ACTGTCCCAG	ACACCAAAGT	TAATTTCTAT	300
GCCTGGAAGA	GGATGGAGGT	CGGGCAGCAG	GCCGTAGAAG	TCTGGCAGGG	CCTGGCCCTG	360
CTGTCGGAAG	CTGTCCTGCG	GGGCCAGGCC	CTGTTGGTCA	ACTCTTCCCA	GCCGTGGGAG	420
CCCCTGCAGC	TGCATGTGGA	TAAAGCCGTC	AGTGGCCTTC	GCAGCCTCAC	CACCTGCTT	480
CGGGCTCTGG	GAGCCCAGAA	GGAAGCCATC	TCC			513

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

CCAGATGCGG	CCTCAGCTGC	TCCACTCCGA	ACAATCACTG	CTGACACTTT	CCGCAAAC	60
TTCCGAGTCT	ACTCCAATTT	CCTCCGGGGA	AAGCTGAAGC	TGTACACAGG	GGAGGCCTGC	120
AGGACAGGGG	ACAGATGAGG	CGGCGGCTCC	CCCCACCACG	CCTCATCTGT	GACAGCCGAG	180

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TCCTGGAGAG	GTACCTCTTG	GAGGCCAAGG	AGGCCGAGAA	TATCACGACG	GGCTGTGCTG	240
AACACTGCAG	CTTGAATGAG	AATAATCACT	GTCCCAGACA	CCAAAGTTAA	TTTCTATGCC	300
TGGAAGAGGA	TGGAGGTCGG	GCAGCAGGCC	GTAGAAGTCT	GGCAGGGCCT	GGCCCTGCTG	360
TCGGAAGCTG	TCCTGCGGGG	CCAGGCCCTG	TTGGTCAACT	CTTCCCAGCC	GTGGGAGCCC	420
CTGCAGCTGC	ATGTGGATAA	AGCCGTCAGT	GGCCTTCGCA	GCCTCACCAC	TCTGCTTCGG	480
GCTCTGGGAG	CCCAGAAGGA	AGCCATCTCC	CCT			513

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

GATGCGGCCT	CAGCTGCTCC	ACTCCGAACA	ATCACTGCTG	ACACTTTCCG	CAAACCTCTT	60
CGAGTCTACT	CCAATTTCTT	CCGGGGAAAG	CTGAAGCTGT	ACACAGGGGA	GGCCTGCAGG	120
ACAGGGGACA	GATGAGGCGG	CGGCTCCCCC	CACCACGCCT	CATCTGTGAC	AGCCGAGTCC	180
TGGAGAGGTA	CCTTTGGAG	GCCAAGGAGG	CCGAGAATAT	CACGACGGGC	TGTGCTGAAC	240
ACTGCAGCTT	GAATGAGAAT	AATCACTGTC	CCAGACACCA	AAGTTAATTT	CTATGCCTGG	300
AAGAGGATGG	AGGTCGGGCA	GCAGGCCGTA	GAAGTCTGGC	AGGGCCTGGC	CCTGCTGTCTG	360
GAAGCTGTCC	TGCGGGGCCA	GGCCCTGTTG	GTCAACTCTT	CCCAGCCGTG	GGAGCCCCTG	420
CAGCTGCATG	TGGATAAAGC	CGTCAGTGGC	CTTCGCAGCC	TCACCACTCT	GCTTCGGGCT	480
CTGGGAGCCC	AGAAGGAAGC	CATCTCCCCT	CCA			513

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

GCGGCCTCAG	CTGCTCCACT	CCGAACAATC	ACTGCTGACA	CTTCCGCAA	ACTCTTCCGA	60
GTCTACTCCA	ATTTCCTCCG	GGGAAAGCTG	AAGCTGTACA	CAGGGGAGGC	CTGCAGGACA	120
GGGGACAGAT	GAGGCGGCGG	CTCCCCCAC	CACGCCTCAT	CTGTGACAGC	CGAGTCCTGG	180
AGAGGTACCT	CTTGGAGGCC	AAGGAGGCCG	AGAATATCAC	GACGGGCTGT	GCTGAACACT	240
GCAGCTTGAA	TGAGAATAAT	CACTGTCCCA	GACACCAAAG	TTAATTTCTA	TGCCTGGAAG	300
AGGATGGAGG	TCGGGCAGCA	GGCCGTAGAA	GTCTGGCAGG	GCCTGGCCCT	GCTGTCCGAA	360
GCTGTCTCTG	GGGGCCAGGC	CCTGTGGTTC	AACTCTTCCC	AGCCGTGGGA	GCCCCTGCAG	420
CTGCATGTGG	ATAAAGCCGT	CAGTGGCCTT	CGCAGCCTCA	CCACTCTGCT	TCGGGCTCTG	480
GGAGCCCAGA	AGGAAGCCAT	CTCCCTCCA	GAT			513

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

GCCTCAGCTG	CTCCACTCCG	AACAATCACT	GCTGACACTT	TCCGCAAAC	CTTCCGAGTC	60
TACTCCAATT	TCCTCCGGGG	AAAGCTGAAG	CTGTACACAG	GGGAGGCCTG	CAGGACAGGG	120
GACAGATGAG	GCGGCGGCTC	CCCCACCAC	GCCTCATCTG	TGACAGCCGA	GTCTGGAGA	180
GGTACCTCTT	GGAGGCCAAG	GAGGCCGAGA	ATATCACGAC	GGGCTGTGCT	GAACACTGCA	240
GCTTGAATGA	GAATAATCAC	TGTCCAGAC	ACCAAAGTTA	ATTTCTATGC	CTGGAAGAGG	300
ATGGAGGTCG	GGCAGCAGGC	CGTAGAAGTC	TGGCAGGGCC	TGGCCCTGCT	GTGGAAGCT	360
GTCCTGCGGG	GCCAGGCCCT	GTTGGTCAAC	TCTTCCAGC	CGTGGGAGCC	CCTGCAGCTG	420
CATGTGGATA	AAGCCGTGAG	TGGCCTTCGC	AGCCTCACCA	CTCTGCTTCG	GGCTCTGGGA	480
GCCCAGAAGG	AAGCCATCTC	CCCTCCAGAT	GCG			513

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

TCAGCTGCTC	CACTCCGAAC	AATCACTGCT	GACACTTTCC	GCAAACTCTT	CCGAGTCTAC	60
TCCAATTTC	TCCGGGGAAA	GCTGAAGCTG	TACACAGGGG	AGGCCTGCAG	GACAGGGGAC	120
AGATGAGGCG	GCGGCTCCCC	CCACCACGCC	TCATCTGTGA	CAGCCGAGTC	CTGGAGAGGT	180
ACCTCTTGGA	GGCCAAGGAG	CCCAGAGAATA	TCACGACGGG	CTGTGCTGAA	CACTGCAGCT	240
TGAATGAGAA	TAATCACTGT	CCCAGACACC	AAAGTTAATT	TCTATGCCTG	GAAGAGGATG	300
GAGGTCGGGC	AGCAGGCCGT	AGAAGTCTGG	CAGGGCCTGG	CCCTGCTGTC	GGAAGCTGTC	360
CTGCGGGGCC	AGGCCCTGTT	GGTCAACTCT	TCCCAGCCGT	GGGAGCCCCC	GCAGCTGCAT	420
GTGGATAAAG	CCGTCACTGG	CCTTCGCAGC	CTCACCCTC	TGCTTCGGG	TCTGGGAGCC	480
CAGAAGGAAG	CCATCTCCCC	TCCAGATGCG	GCC			513

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

GCTGCTCCAC	TCCGAACAAT	CACTGCTGAC	ACTTTCGGCA	AACTCTTCCG	AGTCTACTCC	60
AATTTCTCTC	GGGGAAAGCT	GAAGCTGTAC	ACAGGGGAGG	CCTGCAGGAC	AGGGGACAGA	120
TGAGGCGGCG	GCTCCCCCA	CCAGCCCTCA	TCTGTGACAG	CCGAGTCTTG	GAGAGGTACC	180
TCTTGAGGCG	CAAGGAGGCC	GAGAATATCA	CGACGGGCTG	TGCTGAACAC	TGCAGCTTGA	240
ATGAGAATAA	TCACTGTCCC	AGACACCAAA	GTTAATTTCT	ATGCCTGGAA	GAGGATGGAG	300
GTCCGGCAGC	AGGCCGTAGA	AGTCTGGCAG	GGCCTGGCCC	TGCTGTGGGA	AGCTGTCTCTG	360
CGGGGCCAGG	CCCTGTGGT	CAACTCTTCC	CAGCCGTGGG	AGCCCCTGCA	GCTGCATGTG	420
GATAAAGCCG	TCAGTGGCCT	TGCGAGCCTC	ACCACTCTGC	TTCGGGCTCT	GGGAGCCCAG	480
AAGGAAGCCA	TCTCCCTCTC	AGATGCGGCC	TCA			513

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

GCTCCACTCC	GAACAATCAC	TGCTGACACT	TTCGCAAAAC	TCTTCCGAGT	CTACTCCAAT	60
TTCTTCCGGG	GAAAGCTGAA	GCTGTACACA	GGGGAGGCCCT	GCAGGACAGG	GGACAGATGA	120
GGCGGCGGCT	CCCCCCACCA	CGCCTCATCT	GTGACAGCCG	AGTCCTGGAG	AGGTACCTCT	180
TGGAGGCCAA	GGAGGCCGAG	AATATCACGA	CGGGCTGTGC	TGAACACTGC	AGCTTGAATG	240
AGAATAATCA	CTGTCCCA	CACCAAAGTT	AATTTCTATG	CCTGGAAGAG	GATGGAGGTC	300
GGGCAGCAGG	CCGTAGAAGT	CTGGCAGGGC	TGGGCCCTGC	TGTCGGAAGC	TGTCCTGCGG	360
GGCCAGGCC	TGTTGGTCAA	CTCTTCCAG	CCCTGGGAGC	CCCTGCAGCT	GCATGTGGAT	420
AAAGCCGTCA	GTGGCCTTCG	CAGCCTCACC	ACTCTGCTTC	GGGCTCTGGG	AGCCCAGAAG	480
GAAGCCATCT	CCCCTCCAGA	TGCGGCCTCA	GCT			513

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

CCACTCCGAA	CAATCACTGC	TGACACTTTC	CGCAAACCTCT	TCCGAGTCTA	CTCCAATTTT	60
CTCCGGGGAA	AGCTGAAGCT	GTACACAGGG	GAGGCCTGCA	GGACAGGGGA	CAGATGAGGC	120
GGCGGCTCCC	CCCACCACGC	CTCATCTGTG	ACAGCCGAGT	CCTGGAGAGG	TACCTCTTGG	180
AGGCCAAGGA	GGCCGAGAAT	ATCACGACGG	GCTGTGCTGA	ACACTGCAGC	TTGAATGAGA	240
ATAATCACTG	TCCCAGACAC	CAAAGTTAAT	TTCTATGCCT	GGAAGAGGAT	GGAGGTGCGG	300
CAGCAGGCCG	TAGAAGTCTG	GCAGGGCCTG	GCCTGCTGT	CGGAAGCTGT	CCTGCGGGGC	360
CAGGCCCTGT	TGGTCAACTC	TTCCCAGCCG	TGGGAGCCCC	TGCAGCTGCA	TGTGGATAAA	420
GGCGTCAGTG	GCCTTCGCAG	CCTCACCCT	CTGCTTCGGG	CTCTGGGAGC	CCAGAAGGAA	480
GCCATCTCCC	CTCCAGATGC	GGCCTCAGCT	GCT			513

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(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

CTCCGAACAA	TCACTGCTGA	CACTTTCCGC	AAACTCTTCC	GAGTCTACTC	CAATTTCTCTC	60
CGGGGAAAGC	TGAAGCTGTA	CACAGGGGAG	GCCTGCAGGA	CAGGGGACAG	ATGAGGCGGC	120
GGCTCCCCCC	ACCACGCCTC	ATCTGTGACA	GCCGAGTCCT	GGAGAGGTAC	CTCTTGGAGG	180
CCAAGGAGGC	CGAGAATATC	ACGACGGGCT	GTGCTGAACA	CTGCAGCTTG	AATGAGAATA	240
ATCACTGTCC	CAGACACCAA	AGTTAATTTT	TATGCCTGGA	AGAGGATGGA	GGTCGGGCAG	300
CAGGCCGTAG	AAGTCTGGCA	GGGCCTGGCC	CTGCTGTCCG	AAGCTGTCTT	GCGGGGCCAG	360
GCCCTGTGTT	TCAACTCTTC	CCAGCCGTGG	GAGCCCTGTC	AGCTGCATGT	GGATAAAGCC	420
GTCAGTGGCC	TTCCGAGCCT	CACCACTCTG	CTTCGGGCTC	TGGGAGCCCA	GAAGGAAGCC	480
ATCTCCCCTC	CAGATGCGGC	CTCAGCTGCT	CCA			513

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

CGAACAAATCA	CTGCTGACAC	TTCCGCAAA	CTCTCCGAG	TCTACTCCAA	TTCTCTCCGG	60
GGAAAGCTGA	AGCTGTACAC	AGGGGAGGCC	TGCAGGACAG	GGGACAGATG	AGGCGGCGGC	120
TCCCCCCACC	ACGCCTCATC	TGTGACAGCC	GAGTCCTGGA	GAGGTACCTC	TTGGAGGCCA	180
AGGAGGCCGA	GAATATCACG	ACGGGCTGTG	CTGAACACTG	CAGCTTGAAT	GAGAATAATC	240
ACTGTCCCG	ACACCAAAGT	TAATTTCTAT	GCCTGGAAGA	GGATGGAGGT	CGGGCAGCAG	300
GCCGTAGAAG	TCTGGCAGGG	CCTGGCCCTG	CTGTCCGAAG	CTGTCTGCG	GGGCCAGGCC	360
CTGTGTGGTCA	ACTCTTCCCA	GCCGTGGGAG	CCCCTGCAGC	TGCATGTGGA	TAAAGCCGTC	420
AGTGGCCTTC	GCAGCCTCAC	CACTCTGCTT	CGGGCTCTGG	GAGCCCAGAA	GGAAGCCATC	480
TCCCCCTCCAG	ATGCGGCCTC	AGTGCTCTCA	CTC			513

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 513 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

ACAATCACTG	CTGACACTTT	CCGCAAACTC	TTCCGAGTCT	ACTCCAATTT	CCTCCGGGGA	60
AAGCTGAAGC	TGTACACAGG	GGAGGCCTGC	AGGACAGGGG	ACAGATGAGG	CGGCGGCTCC	120
CCCCACCACG	CCTCATCTGT	GACAGCCGAG	TCCTGGAGAG	GTACCTCTTG	GAGGCCAAGG	180
AGGCCGAGAA	TATCACGACG	GGCTGTGCTG	AACACTGCAG	CTTGAATGAG	AATAATCACT	240
GTCCCAGACA	CCAAAGTTAA	TTTCTATGCC	TGGAAGAGGA	TGGAGGTCGG	GCAGCAGGCC	300
GTAGAAGTCT	GGCAGGGCCT	GGCCCTGCTG	TCGGAAGCTG	TCCTGCCGGG	CCAGGCCCTG	360
TTGGTCAACT	CTTCCAGGCC	GTGGGAGCCC	CTGCAGCTGC	ATGTGGATAA	AGCCGTCAGT	420
GGCCTTCGCA	GCCTCACCAC	TCTGCTTCGG	GCTCTGGGAG	CCCAGAAGGA	AGCCATCTCC	480
CCTCCAGATG	CGGCCTCAGC	TGCTCCACTC	CGA			513

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 501 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

GCCCCACCAC	GCCTCATCTG	TGACAGCCGA	GTCCTGGAGA	GGTACCTCTT	GGAGGCCAAG	60
GAGGCCGAGA	ATATCACGAC	GGGCTGTGCT	GAACACTGCA	GCTTGAATGA	GAATATCACT	120
GTCCCAGACA	CCAAAGTTAA	TTTCTATGCC	TGGAAGAGGA	TGGAGGTCGG	GCAGCAGGCC	180

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GTAGAAGTCT	GGCAGGGCCT	GGCCCTGCTG	TCCGAAGCTG	TCCTGCGGGG	CCAGGCCCTG	240
TTGGTCAACT	CTTCCCAGCC	GTGGGAGCCC	CTGCAGCTGC	ATGTGGATAA	AGCCGTCAGT	300
GGCCTTCGCA	GCCTCACCAC	TCTGCTTCGG	GCTCTGGGAG	CCCAGAAGGA	AGCCATCTCC	360
CCTCCAGATG	CGGCCTCAGC	TGCTCCACTC	CGAACAATCA	CTGCTGACAC	TTTCCGCAAA	420
CTCTTCCGAG	TCTACTCCAA	TTTCTCCCG	GGAAAGCTGA	AGCTGTACAC	AGGGGAGGCC	480
TGCAGGACAG	GGGACAGATG	A				501

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 166 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Ala	Pro	Pro	Arg	Leu	Ile	Cys	Asp	Ser	Arg	Val	Leu	Glu	Arg	Tyr	Leu
1				5					10					15	
Leu	Glu	Ala	Lys	Glu	Ala	Glu	Asn	Ile	Thr	Thr	Gly	Cys	Ala	Glu	His
			20				25						30		
Cys	Ser	Leu	Asn	Glu	Asn	Ile	Thr	Val	Pro	Asp	Thr	Lys	Val	Asn	Phe
		35				40					45				
Tyr	Ala	Trp	Lys	Arg	Met	Glu	Val	Gly	Gln	Gln	Ala	Val	Glu	Val	Trp
	50				55				60						
Gln	Gly	Leu	Ala	Leu	Leu	Ser	Glu	Ala	Val	Leu	Arg	Gly	Gln	Ala	Leu
65				70					75					80	
Leu	Val	Asn	Ser	Ser	Gln	Pro	Trp	Glu	Pro	Leu	Gln	Leu	His	Val	Asp
			85					90					95		
Lys	Ala	Val	Ser	Gly	Leu	Arg	Ser	Leu	Thr	Thr	Leu	Leu	Arg	Ala	Leu
			100				105						110		
Gly	Ala	Gln	Lys	Glu	Ala	Ile	Ser	Pro	Pro	Asp	Ala	Ala	Ser	Ala	Ala
		115					120				125				
Pro	Leu	Arg	Thr	Ile	Thr	Ala	Asp	Thr	Phe	Arg	Lys	Leu	Phe	Arg	Val
	130					135					140				
Tyr	Ser	Asn	Phe	Leu	Arg	Gly	Lys	Leu	Lys	Leu	Tyr	Thr	Gly	Glu	Ala
145				150					155					160	
Cys	Arg	Thr	Gly	Asp	Arg										
				165											

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Thr	Val	Pro	Asp	Thr	Lys	Val	Asn	Phe	Tyr	Ala	Trp	Lys	Arg	Met	Glu
1				5					10					15	
Val	Gly	Gln	Gln	Ala	Val	Glu	Val	Trp	Gln	Gly	Leu	Ala	Leu	Leu	Ser
			20					25					30		
Glu	Ala	Val	Leu	Arg	Gly	Gln	Ala	Leu	Leu	Val	Asn	Ser	Ser	Gln	Pro
		35				40					45				
Trp	Glu	Pro	Leu	Gln	Leu	His	Val	Asp	Lys	Ala	Val	Ser	Gly	Leu	Arg
	50				55				60						
Ser	Leu	Thr	Thr	Leu	Leu	Arg	Ala	Leu	Gly	Ala	Gln	Lys	Glu	Ala	Ile
65				70					75					80	
Ser	Pro	Pro	Asp	Ala	Ala	Ser	Ala	Ala	Pro	Leu	Arg	Thr	Ile	Thr	Ala
			85					90					95		
Asp	Thr	Phe	Arg	Lys	Leu	Phe	Arg	Val	Tyr	Ser	Asn	Phe	Leu	Arg	Gly
			100				105					110			
Lys	Leu	Lys	Leu	Tyr	Thr	Gly	Glu	Ala	Cys	Arg	Thr	Gly	Asp	Arg	Gly
		115				120					125				
Gly	Gly	Ser	Ala	Pro	Pro	Arg	Leu	Ile	Cys	Asp	Ser	Arg	Val	Leu	Glu
	130					135					140				
Arg	Tyr	Leu	Leu	Glu	Ala	Lys	Glu	Ala	Glu	Asn	Ile	Thr	Thr	Gly	Cys
145				150					155					160	
Ala	Glu	His	Cys	Ser	Leu	Asn	Glu	Asn	Ile						
				165					170						

(2) INFORMATION FOR SEQ ID NO:123:

90

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Gly Gly Gly Ser

1

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Gly Gly Gly Ser Gly Gly Gly Ser

1

5

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser

1

5

10

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Ser Gly Gly Ser Gly Gly Ser

1

5

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Glu Phe Gly Asn Met

1

5

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 6 amino acids

91

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Glu Phe Gly Gly Asn Met
1 5

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 9 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Glu Phe Gly Gly Asn Gly Gly Asn Met
1 5

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: None

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Gly Gly Ser Asp Met Ala Gly
1 5

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

GCGCGCCCAT GGACAATCAC TGCTGAC

27

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

TCTGTCCCCT GTCCT

15

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

92

GCGCGCAAGC TTATTATCGG AGTGGAGCAG CTGAGGCCGC ATC

43

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

GCCCCACCAC GCCTCATCTG T

21

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WHAT IS CLAIMED IS:

1. A human EPO receptor agonist polypeptide,
comprising a modified EPO amino acid sequence of the
Formula:

AlaProProArgLeuIleCysAspSerArgValLeuGluArgTyrLeuLeuGluAlaLys
10 20

GluAlaGluAsnIleThrThrGlyCysAlaGluHisCysSerLeuAsnGluAsnIleThr
10 30 40

ValProAspThrLysValAsnPheTyrAlaTrpLysArgMetGluValGlyGlnGlnAla
15 50 60

ValGluValTrpGlnGlyLeuAlaLeuLeuSerGluAlaValLeuArgGlyGlnAlaLeu
70 80

LeuValAsnSerSerGlnProTrpGluProLeuGlnLeuHisValAspLysAlaValSer
20 90 100

GlyLeuArgSerLeuThrThrLeuLeuArgAlaLeuGlyAlaGlnLysGluAlaIleSer
110 120

ProProAspAlaAlaSerAlaAlaProLeuArgThrIleThrAlaAspThrPheArgLys
25 130 140

LeuPheArgValTyrSerAsnPheLeuArgGlyLysLeuLysLeuTyrThrGlyGluAla
150 160

30 CysArgThrGlyAspArg SEQ ID NO:121
166

wherein optionally 1-6 amino acids from the N-
terminus and 1-5 from the C-terminus can be deleted
from said EPO receptor agonist polypeptide;

wherein the N-terminus is joined to the C-terminus
directly or through a linker capable of joining the
N-terminus to the C-terminus and having new C- and N-
termini at amino acids;

23-24	48-49	111-112
24-25	50-51	112-113
25-26	51-52	113-114
26-27	52-53	114-115
27-28	53-54	115-116
28-29	54-55	116-117
29-30	55-56	117-118
30-31	56-57	118-119

	94	
31-32	57-58	119-120
32-33	77-78	120-121
33-34	78-79	121-122
34-35	79-80	122-123
35-36	80-81	123-124
36-37	81-82	124-125
37-38	82-83	125-126
38-39	84-85	126-127
40-41	85-86	127-128
41-42	86-87	128-129
43-44	87-88	129-130
44-45	88-89	130-131
45-46	108-109	131-132
46-47	109-110	respectively; and
47-48	110-111	

said EPO receptor agonist polypeptide may optionally be immediately preceded by (methionine⁻¹), (alanine⁻¹) or (methionine⁻², alanine⁻¹).

5

2. The EPO receptor agonist polypeptide, as recited in claim 1, wherein said linker is selected from the group consisting of;

- 10 GlyGlyGlySer SEQ ID NO:123;
 GlyGlyGlySerGlyGlyGlySer SEQ ID NO:124;
 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID NO:125;
 SerGlyGlySerGlyGlySer SEQ ID NO:126;
 15 GluPheGlyAsnMet SEQ ID NO:127;
 GluPheGlyGlyAsnMet SEQ ID NO:128;
 GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:129; and
 GlyGlySerAspMetAlaGly SEQ ID NO:130.

- 20 3. The EPO receptor agonist polypeptide of claim 1 selected from the group consisting of;
 SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7;
 SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17; SEQ ID NO:18; SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:22; SEQ ID NO:23; SEQ ID NO:24; SEQ ID NO:25; SEQ ID
- 25

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5 NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID
NO:29; SEQ ID NO:30; SEQ ID NO:31; SEQ ID
NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID
NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID
NO:38; SEQ ID NO:39; SEQ ID NO:40; SEQ ID
NO:41; SEQ ID NO:42; SEQ ID NO:43; SEQ ID
NO:44; SEQ ID NO:45; SEQ ID NO:46; SEQ ID
NO:47; SEQ ID NO:48; SEQ ID NO:49; SEQ ID
10 NO:50; SEQ ID NO:51; SEQ ID NO:52; SEQ ID
NO:53; SEQ ID NO:54; SEQ ID NO:55; SEQ ID
NO:56; SEQ ID NO:57; SEQ ID NO:58; SEQ ID
NO:59 and SEQ ID NO:122.

4. The EPO receptor agonist polypeptide of
15 claim 3 wherein the linker sequence (GlyGlyGlyGlySer
SEQ ID NO:123) is replaced by a linker sequence
selected from the group consisting of;

GlyGlyGlySerGlyGlyGlySer SEQ ID NO:124;
20 GlyGlyGlySerGlyGlyGlySerGlyGlyGlySer SEQ ID
NO:125;
SerGlyGlySerGlyGlySer SEQ ID NO:126;
GluPheGlyAsnMet SEQ ID NO:127;
GluPheGlyGlyAsnMet SEQ ID NO:128;
25 GluPheGlyGlyAsnGlyGlyAsnMet SEQ ID NO:129; and
GlyGlySerAspMetAlaGly SEQ ID NO:130.

5. A nucleic acid molecule comprising a DNA
sequence encoding the EPO receptor agonist
30 polypeptide of claim 1.

6. A nucleic acid molecule comprising a DNA
sequence encoding the EPO receptor agonist
polypeptide of claim 2.

35

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7. A nucleic acid molecule comprising a DNA sequence encoding the EPO receptor agonist polypeptide of claim 3.

5 8. A nucleic acid molecule comprising a DNA sequence encoding the EPO receptor agonist polypeptide of claim 3 selected from the group consisting of;

10 SEQ ID NO:60; SEQ ID NO:61; SEQ ID NO:62; SEQ ID NO:63; SEQ ID NO:64; SEQ ID NO:65; SEQ ID NO:66; SEQ ID NO:67; SEQ ID NO:68; SEQ ID NO:69; SEQ ID NO:70; SEQ ID NO:71; SEQ ID NO:72; SEQ ID NO:73; SEQ ID NO:74; SEQ ID NO:75; SEQ ID NO:76; SEQ ID NO:77; SEQ ID NO:78; SEQ ID NO:79; SEQ ID NO:80; SEQ ID NO:81; SEQ ID NO:82; SEQ ID NO:83; SEQ ID NO:84; SEQ ID NO:85; SEQ ID NO:86; SEQ ID NO:87; SEQ ID NO:88; SEQ ID NO:89; SEQ ID NO:90; SEQ ID NO:91; SEQ ID NO:92; SEQ ID NO:93; SEQ ID NO:94; SEQ ID NO:95; SEQ ID NO:96; SEQ ID NO:97; SEQ ID NO:98; SEQ ID NO:99; SEQ ID NO:100; SEQ ID NO:101; SEQ ID NO:102; SEQ ID NO:103; SEQ ID NO:104; SEQ ID NO:105; SEQ ID NO:106; SEQ ID NO:107; SEQ ID NO:108; SEQ ID NO:109; SEQ ID NO:110; SEQ ID NO:111; SEQ ID NO:112; SEQ ID NO:113; SEQ ID NO:114; SEQ ID NO:115; SEQ ID NO:116; SEQ ID NO:117; SEQ ID NO:118 and SEQ ID NO:119.

30 9. A nucleic acid molecule comprising a DNA sequence encoding the EPO receptor agonist polypeptide of claim 4.

35 10. A method of producing a EPO receptor agonist polypeptide comprising: growing under suitable nutrient conditions, a host cell transformed or transfected with a replicable vector comprising said nucleic acid molecule of claim 5, 6, 7, 8 or 9

in a manner allowing expression of said EPO receptor agonist polypeptide and recovering said EPO receptor agonist polypeptide.

5 11. A composition comprising; a EPO receptor agonist polypeptide according to claim 1, 2, 3 or 4; and a pharmaceutically acceptable carrier.

10 12. A composition comprising; a EPO receptor agonist polypeptide according to claim 1, 2, 3 or 4; a factor; and a pharmaceutically acceptable carrier.

15 13. The composition of claim 12 wherein said factor is selected from the group consisting of: GM-CSF, G-CSF, c-mpl ligand, M-CSF, IL-1, IL-4, IL-2, IL-3, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, LIF, flt3/flk2 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem
20 cell factor, IL-3 variants, fusion proteins, G-CSF receptor agonists, c-mpl receptor agonists, IL-3 receptor agonists, multi-functional receptor agonists.

25 14. A method of stimulating the production of hematopoietic cells in a patient comprising the step of; administering a EPO receptor agonist polypeptide of claim 1, 2, 3 or 4, to said patient.

30 15. A method for selective ex vivo expansion of erythroid progenitors, comprising the steps of;
 (a) culturing erythroid progenitor cells in a culture medium, comprising; a polypeptide of claim 1, 2, 3 or 4; and
35 (b) harvesting said cultured cells.

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16. A method for selective ex vivo expansion of erythroid progenitors, comprising the steps of;

(a) separating erythroid progenitor cells from other cells;

5 (b) culturing said separated erythroid progenitor cells with a selected culture medium comprising a polypeptide of claim 1, 2, 3 or 4; and

(c) harvesting said cultured cells.

10 17. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of;

(a) removing erythroid progenitor cells;

(b) culturing said erythroid progenitor cells in a culture medium, comprising; a polypeptide of claim
15 1, 2, 3 or 4;

(c) harvesting said cultured cells; and

(d) transplanting said cultured cells into said patient.

20 18. A method for treatment of a patient having a hematopoietic disorder, comprising the steps of;

(a) removing erythroid progenitor cells;

(b) separating erythroid progenitor cells from other cells;

25 (c) culturing said separated erythroid progenitor cells with a selected culture medium comprising a polypeptide of claim 1, 2, 3 or 4;

(d) harvesting said cultured cells; and

(e) transplanting said cultured cells into said
30 patient.

19. A method of claim 15 wherein said erythroid progenitor cells are isolated from peripheral blood.

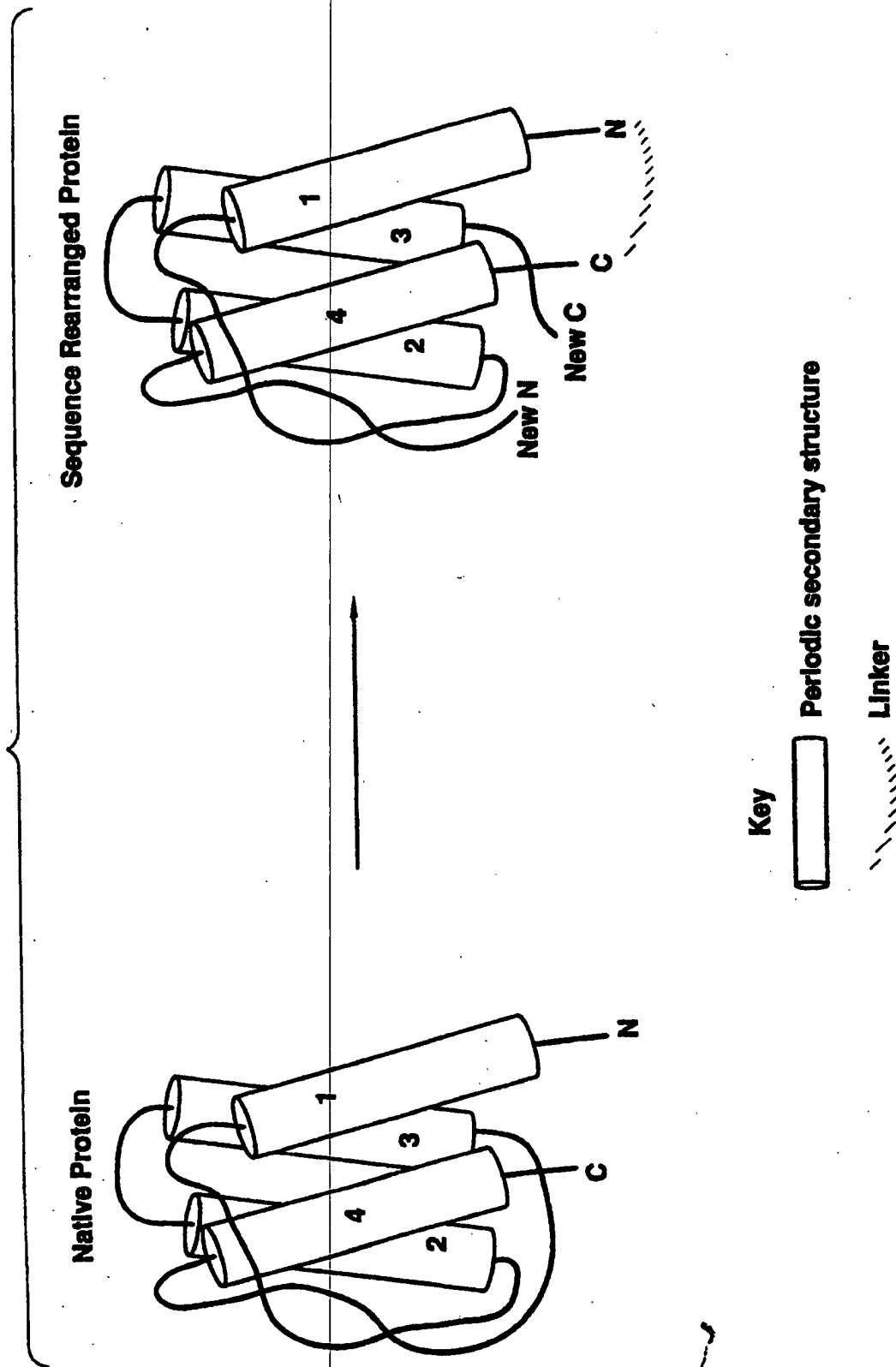
35 20. A method of claim 16 wherein said erythroid progenitor cells are isolated from peripheral blood.

99

21. A method of claim 17 wherein said erythroid progenitor cells are isolated from peripheral blood.

22. A method of claim 18 wherein said erythroid
5 progenitor cells are isolated from peripheral blood.

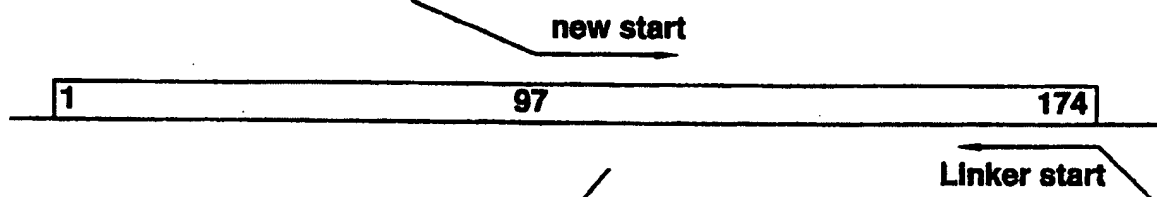
FIG.1



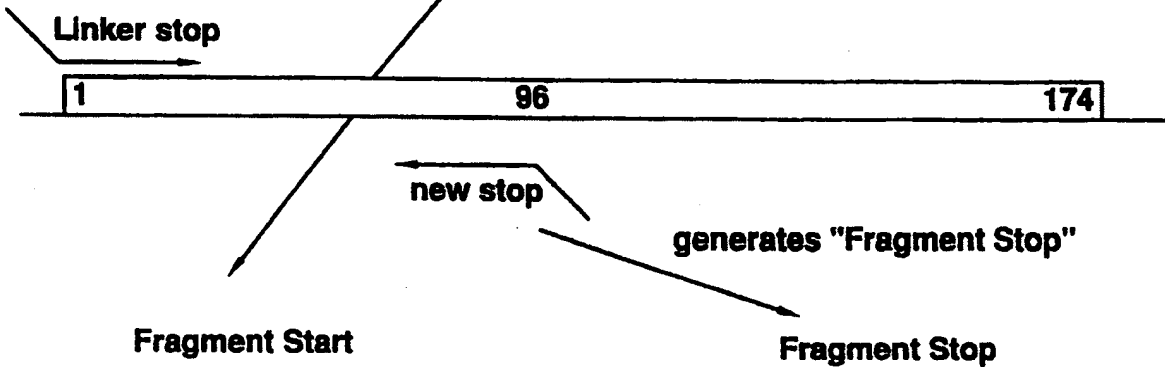
2 / 6

FIG.2

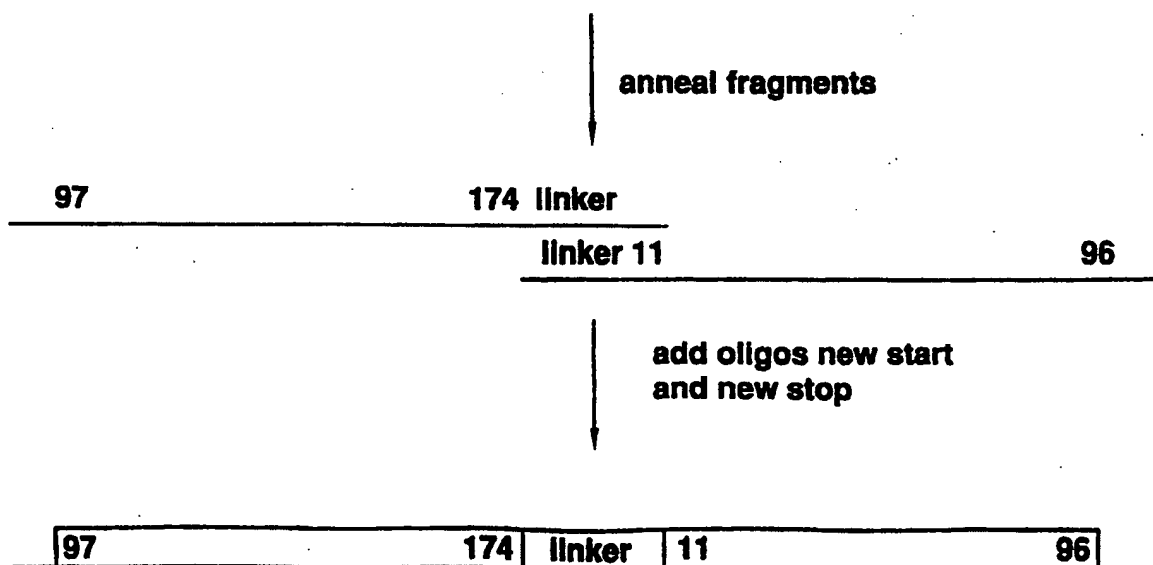
first step PCR amplification



second step PCR amplification



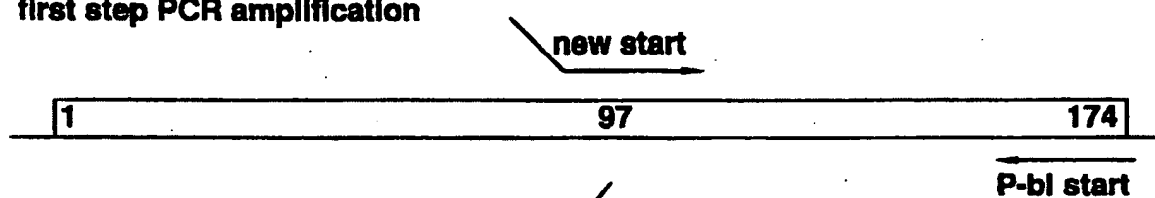
third step PCR amplification



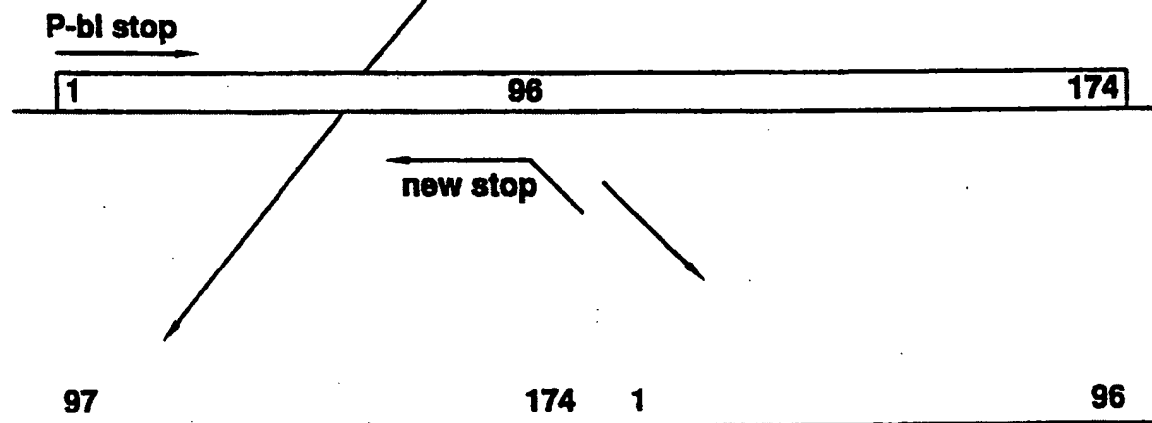
3 / 6

FIG.3

first step PCR amplification



second step PCR amplification



ligate fragments



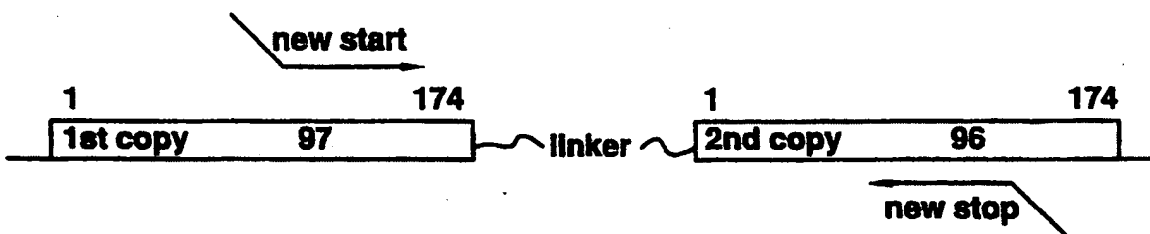
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FIG.4

I. Construct tandemly-duplicated template



II. PCR-amplify tandemly-duplicated template



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1 G C C C C A C C A G C C T C A T C T G T G A C A G C C G A G T C C T G G A G A G T A C C T C T T G G A G G C C A A G 60
C G G G T G G T C G G A G T A G A C A C T G T C G G C T C A G G A C C T C T C C A T G G A G A A C C T C C G G T T C
A l a P r o A r g L e u I l e C y s A s p S e r A r g V a l L e u G l u A r g T y r L e u L e u G l u A l a L y s
61 G A G C C G A G A A T A T C A C G A C G G C T G T G C T G A A C A C T G C A G C T T G A A T G A G A A T A T C A C T 120
C T C C G G C T C T T A T A G T G T G C C C G A C A C G A C T T G T G A C G T C G A A C T T A C T C T T A T A G T G A
G l u A l a G l u A s n I l e T h r T h r G l y C y s A l a G l u H i s C y s S e r L e u A s n G l u A s n I l e T h r
121 G T C C C A G A C A C C A A G T T A A T T T C T A T G C C C T G G A A G A G G A T G G A G G T C G G G C A G C A G G C C 180
C A G G G T C T G T G G T T T C A A T T A A A G A T A C G G A C C T T C T C C T A C C T C C A G C C C G T C G T C C G G
V a l P r o A s p T h r L y s V a l A s n P h e T y r A l a T r p L y s A r g M e t G l u V a l G l y G l n G l n A l a
181 G T A G A A G T C T G G C A G G C C C T G G C C C T G C T G T C G G A A G C T G T C C T G C G G G G C C A G G C C C T G 240
C A T C T T C A G A C C G T C C C G G A C C G G A C G A C A G C C T T C G A C A G G A C G C C C C G T C C G G G A C
V a l G l u V a l T r p G l n G l y L e u A l a L e u L e u S e r G l u A l a V a l L e u A r g G l y G l n A l a L e u
241 T T G G T C A A C T C T T C C C A G C C C G T G G G A G C C C C T G C A G C T G C A T G T G G A T A A A G C C C G T C A G T 300
A A C C A G T T G A G A A G G T C G G C A C C C T C G G G G A C G T C G A C G T A C A C C T A T T T C G G C A G T C A
L e u V a l A s n S e r S e r G l n P r o T r p G l u P r o L e u G l n L e u H i s V a l A s p L y s A l a V a l S e r

FIG. 5B

301 GGCCTTCGCAGCCTCACCACTCTGCTTCGGGCTCTGGGAGCCAGAAAGCAATCTCC
 +-----+-----+-----+-----+-----+-----+ 360
 +-----+-----+-----+-----+-----+-----+
 CCGGAAGCGTCGGAGTGGTGAACGAGCCGAGACCCCTCGGGTCTTCCTTCGGTAGAGG
 GlyLeuArgSerLeuThrThrLeuLeuArgAlaLeuGlyAlaGlnLysGluAlaIleSer
361 CCTCCAGATGCGGCCTCAGCTGCTCCACTCCGAAACAATCACTGCTGACACTTTCGCAAA
 +-----+-----+-----+-----+-----+-----+ 420
 +-----+-----+-----+-----+-----+-----+
 GGAGTCTACGCCGGAGTCGACGAGGTGAGGCTTGTTAGTGACGACTGTGAAGCGGTTT
 ProProAspAlaAlaSerAlaAlaProLeuArgThrIleThrAlaAspThrPheArgLys
421 CTCTTCCGAGTCTACTCCAATTTCCTCCGGGAAAGCTGAAGCTGTACACAGGGAGGCC
 +-----+-----+-----+-----+-----+-----+ 480
 +-----+-----+-----+-----+-----+-----+
 GAGAAGGCTCAGATGAGGTTAAAGGAGGCCCTTTCGACTTCGACATGTGTCCCTCCCG
 LeuPheArgValTyrSerAsnPheLeuArgGlyLysLeuLysLeuTyrThrGlyGluAla
481 TGCAGGACAGGGACAGATGA
 +-----+-----+-----+-----+-----+-----+ 501
 +-----+-----+-----+-----+-----+-----+
 ACGTCCTGTCCCCCTGTCTACT
 CysArgThrGlyAspArg

INTERNATIONAL SEARCH REPORT

Int Application No
PCT/US 97/18703

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/18 C07K14/505 C07K14/52 A61K38/18 C12N5/10
C12N5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 27732 A (US HEALTH ;PASTAN IRA (US); KREITMAN ROBERT J (US)) 19 October 1995 see abstract; claims 1-51; figures SEQ.54-57 ---	1-13,15, 16,19-22
Y	WO 92 06116 A (ORTHO PHARMA CORP) 16 April 1992 see page 2, paragraph 3; claims 1-26; figure SEQ.3 ---	1-13,15, 16,19-22
A	VIGUERA AR ET AL: "The order of secondary structure elements does not determine the structure of a protein but does affect its folding kinetics." J MOL BIOL, APR 7 1995, 247 (4) P670-81, ENGLAND, XP002056595 cited in the application see the whole document ---	1-11
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

23 February 1998

Date of mailing of the international search report

1 1. 03 98

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Gurdjian, D

INTERNATIONAL SEARCH REPORT

Int

Application No

PCT/US 97/18703

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HORLICK R A ET AL: "PERMUTEINS OF INTERLEUKIN 1 BETA-A SIMPLIFIED APPROACH FOR THE CONSTRUCTION OF PERMUTATED PROTEINS HAVING NEW TERMINI" PROTEIN ENGINEERING, vol. 5, no. 5, 1992, pages 427-431, XP002022097 see the whole document ---	1-13
A	KREITMAN R J ET AL: "A CIRCULARLY PERMUTED RECOMBINANT INTERLEUKIN 4 TOXIN WITH INCREASED ACTIVITY" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 91, no. 15, July 1994, pages 6889-6893, XP002022099 see the whole document ---	1-13
A	WO 95 21197 A (SEARLE & CO ;BAUER CHRISTOPHER S (US); ABRAMS MARK ALLEN (US); BRA) 10 August 1995 see page 1 - page 33 -----	1-13,15, 16,19-22

INTERNATIONAL SEARCH REPORT

Int. application No.
PCT/US 97/18703

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97/18703

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 14 17 18 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In. Application No

PCT/US 97/18703

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